HYBRID ENDOTRACHEAL TUBES

By

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Abstract of Dissertation Presented to the Graduate School
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Intubation involves the placement of a tube into the tracheal lumen and is prescribed in any setting in which the airway must be stabilized or the patient anesthetized. The purpose of the endotracheal tube in these procedures is to maintain a viable airway, facilitate mechanical ventilation, allow the administration of anesthetics, and prevent the reflux of vomitus into the lungs. In order to satisfy these requirements a nearly airtight seal must be maintained between the tube and the tracheal lining. Most conventional endotracheal tubes provide this seal by employing a cuff that is inflated once the tube is in place. However, the design of this cuff and properties of the material are a source of irritation and injury to the tracheal tissues. In fact, the complication rate for endotracheal intubation is reported to be between 10 and 60%, with manifestations ranging from severe sore throat to erosion through

the tracheal wall. These complications are caused by a combination of the materials employed and the forces exerted by the cuff on the tracheal tissues. In particular, the abrasive action of the cuff shears cells from the lining, epithelium adhering to the cuff is removed during extubation, and normal forces exerted on the basement tissues disrupt the blood supply and cause pressure necrosis.

The complications associated with tracheal intubation may be reduced or eliminated by employing airway devices constructed from hydrogel materials. Hydrogels are a class of crosslinked polymers which swell in the presence of moisture, and may contain more than 95% water by weight. For the current study, several prototype airway devices were constructed from hydrogel materials including poly(vinyl alcohol), poly(hydroxyethyl methacrylate), and poly(vinyl pyrrolidone). The raw hydrogel materials from this group were subjected to tensile, swelling, and biocompatibility testing, while the finished devices were subjected to extensive mechanical simulation and animal trials. During the course of these experiments it was discovered that reduced water content hydrogel materials generally exhibited superior mechanical properties, but performed more poorly during simulation and biocompatibility studies. Conversely, higher water content materials exhibited lower mechanical performance but superior simulation and biocompatibility results.

CHAPTER 1
ENDOTRACHEAL INTUBATION

1.1 Background

1.1.1 History

The first modern use of an artificial airway is generally attributed to Desault, who in 1820 accidentally instilled bouillon into a patient's trachea through a misplaced feeding tube.[1] While unfortunate for the patient, this serendipitous event allowed the development of a method for treating airway blockage, which prior to this time was usually fatal. Desault's device was only a simple rubber tube but was successfully employed as an artificial airway until 1869, when Trendelenburg improved the design by the addition of a small balloon.[2] This could be inflated to create a nearly airtight seal with the tracheal lumen, allowing more efficient respiration and affording some protection against the aspiration of fluids. This device was used extensively until 1893, when Eisenmenger proposed replacing Trendelenburg's balloon with a longer, thinner-walled design.

Eisenmenger recognized tracheal injuries following extubation and hypothesized a relationship with excessive sealing pressure. He believed that a larger balloon would reduce injury by distributing the seal over a greater area, thereby decreasing the forces applied to the tracheal tissues at any given point.[3] However, most scientists of this time did not yet fully

understand or even acknowledge the complications associated with tracheal intubation. Early clinicians were inclined to discount these problems because airway tubes were recognized as life-saving devices and no alternative technologies were available. These devices had already proven vitally important in treating airway obstruction during the American Civil War and the diphtheria epidemic of the late 19th century. As a result, the importance of Eisenmenger's development was not immediately recognized or widely adopted for another seventy years. Many design variations were suggested during this time period, but Eisenmenger's basic design was not truly utilized until the 1960s.

In modern times the artificial airway has been proven a medical necessity. Still, many health care providers take these devices for granted and overlook airway maintenance as an essential part of patient care. This is unfortunate because almost all surgical, emergency, and critical care procedures begin with the maintenance of the airway. The survival of the patient is dependent on respiration, so if the passage to the lungs is blocked the patient will expire within minutes. In addition, many surgical procedures require the reliable administration and maintenance of inhalational anesthetics. With this in mind an artificial airway may be defined generically as any device designed primarily to maintain an open and secure passage to the lungs. By definition these devices must permit mechanical ventilation, while some may provide additional protection against airway blockage or fluid aspiration. Depending on the application this device may be a laryngeal mask, a nasopharyngeal tube, or an endotracheal tube. Modern surgical procedures requiring general anesthesia normally employ some type of endotracheal tube.

1.1.2 Endotracheal Tubes

More than twenty million procedures involving endotracheal intubation are performed each year in the United States.[4] This procedure involves the placement (Figure 1.1) of a tube into the tracheal lumen and is prescribed in any setting in which the airway must be stabilized or the subject anesthetized. The purpose of the endotracheal tube in these procedures is to maintain a viable airway, facilitate mechanical ventilation, allow the administration of anesthetics, and prevent the reflux of vomitus into the lungs. In order to satisfy these requirements a nearly airtight seal must be maintained between the tube and the tracheal lining. Most conventional endotracheal tubes provide this seal by employing a balloon or 'cuff' that is inflated once the tube is in place.

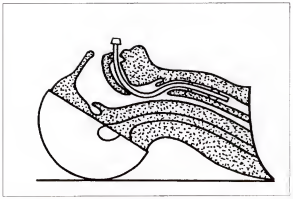

Figure 1.1 Endotracheal intubation with the tube properly positioned and the cuff inflated.

There are three types of modern endotracheal tube based on the original designs of Desault, Trendelenburg, and Eisenmenger. These are normally constructed from transparent polyvinyl chloride (PVC) plastic and may be employed with or without an integral cuff. The uncuffed airway tube (Figure 1.2a) pioneered by Desault is no longer used on adult patients. This tube offers minimal protection against the aspiration of fluids and the absence of a cuff usually prevents a reliable seal from being established. Since a lack of seal precludes the safe use of inhalational anesthetics, the application of uncuffed tubes is primarily restricted to neonates and small children.

Cuffed endotracheal tubes employing a variation of the Trendelenburg balloon are known in modern terminology as low-volume (Figure 1.2b) cuffed tubes. These devices feature a small, spherical cuff that is capable of safely maintaining seal under certain low-pressure conditions. At greater airway pressures the cuff must be over-inflated to maintain adequate seal, deforming the lumen and compressing the fragile tracheal tissues. In spite of this shortcoming these devices still see limited use in some applications. They have fallen from favor since the 1960s however, when clinical evidence first suggested that the cuff design was a contributing factor in tracheal injuries.[1,3]

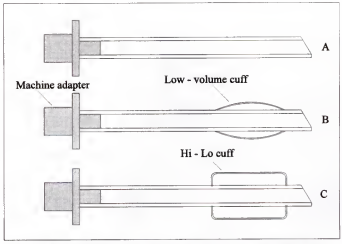

Figure 1.2 The three types of modern endotracheal tube. Hi-Lo cuffed tubes are the airway device of choice because of reduced complication rates.

Most modern endotracheal tubes employ a variation of the Eisenmenger cuff (Figure 1.2c) and are commonly known as high-volume, low-pressure, or square-cuffed tubes. Square-cuffed endotracheal tubes represent the current state of the art and are the device most commonly employed today for airway management. Similar to other airway devices, the semi-rigid tube maintains airway viability while the inflated cuff creates the seal and helps to prevent fluid aspiration. The advantage of this design is the increased contact area of the cuff, which in theory reduces the forces applied to the tracheal tissues by distributing the sealing pressure over a larger surface area. Most scientists agree that this approach should reduce injuries associated with applied cuff pressure.

1.1.3 Mechanical Ventilation

Many critical care scenarios require mechanical ventilation. Aside from the obvious mission of airway maintenance, whenever the function of the autonomic nervous system is compromised due to coma, spinal injury, or general anesthesia mechanical ventilation is a necessity. Under these conditions the patient will typically be intubated with an endotracheal or tracheotomy tube and connected to a mechanical ventilator to stabilize and maintain respiration while the condition persists or the procedure continues. Patients who simply have difficulty breathing due to illness or distress may be masked, but situations involving general anesthesia will almost always involve intubation. A competent medical technician will then monitor the vital signs of the patient.

The condition of the lungs affects airway pressure and is considered by the physician in determining the method of anesthesia and ventilation. One method of characterizing lung condition is with compliance. Lung compliance is a term which describes the impedance of the lung to inflation, a highly compliant lung being one that is easily inflated at lower pressures. Most young and healthy people have lungs in this condition. However, lung compliance decreases with age and infirmity, so an elderly or sick patient will normally have lower compliance or 'stiff' lungs. Lungs may also become stiff with fluid accumulation, pneumonia, or trauma. In these situations the ventilation pressure must be increased to overcome the lung impedance, increasing the possibility of airway injuries.

To contain airway pressure and ventilate the patient a seal must be created between the endotracheal tube and the tracheal lining. To maintain this seal with minimal leakage the pressure in the cuff must equal or exceed the airway pressure. This is problematic because

the cuff pressure is exerted directly on the tracheal lining. Since it has been clinically established that high cuff-to-trachea (CT) pressures contribute to tissue damage, it follows that injury to these tissues is more likely to occur under low-compliance conditions.[3,5,6] This situation is particularly troublesome because the presence of cuff-related tracheal injury helps to create a pathway for bacterial invasion. Because many of these patients are stressed, elderly, or immuno-compromised to begin with, it is very easy for serious or even life-threatening illnesses to develop. Ventilator-associated pneumonia is an unfortunate side effect and frequent cause of death for many of these patients.[5]

1.1.4 The Trachea

The trachea serves primarily to provide a passage between the larynx and the branching of the main stream bronchi. However, the trachea is not a simple conduit to the lungs, but a complex structure that may be divided conceptually into three parts. These are the superstucture, the basement tissues, and the mucosal lining. The first of these, the superstructure is composed of open-ended hyaline cartilage rings (Figure 1.3) connected longitudinally by smooth muscle tissue. These cartilage rings are often described as c-shaped, with the gap between the cartilage tips closed by the Trachealis muscle. This muscle modulates the gap and allows for the expansion and contraction of the

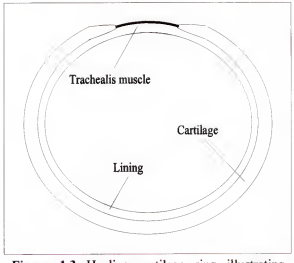

Figure 1.3 Hyaline cartilage ring illustrating position of trachealis muscle.

trachea that occurs during respiration. The overall framework is solid enough to provide mechanical integrity, maintain the roughly cylindrical shape of the lumen, and still allow the flexibility required by motion of the neck and head.

The basement tissues (Figure 1.4) anchor the trachea in the neck and provide a cushion between the rigid cartilage rings and the softer lining. These tissues also supply blood to the trachea and adjacent areas. The basement tissues are soft and spongy so blood flow may be influenced by tissue compression, particularly in the region overlying the cartilage rings. If blood flow is compromised, even temporarily, tissue damage may occur.

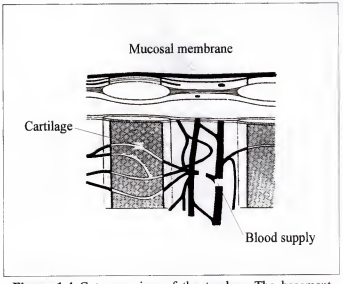

Figure 1.4 Cutaway view of the trachea. The basement tissues provide blood flow to the trachea tissues.

The mucosa overlays the basement tissues and is composed primarily of ciliated epithelium and goblet cells. The goblet cells secrete a thick and sticky mucous which keeps the lining moist and serves to entrap inhaled and resident particulate matter. The beating of the cilia then carries this matter to the base of the larynx, where it is swallowed or expelled. The mucosal lining is possibly the most important component of the tracheal structure, because it forms a barrier against bacterial invasion and prevents fluid from accumulating in the lungs. Unfortunately, this is also the tissue most affected by the airway device.

1.2 Complications with Intubation

1.2.1 Factors in Injury

The invention of the square cuff was a tremendous advance for airway management. Physicians of the late 19th century did not yet know better, but during this time low-volume cuffs were responsible for a significant number of injuries to the trachea. Still, the square cuff did not solve these problems, because the complication rate for endotracheal intubation is reportedly between 10 and 60%.[3,7,8,9] Manifestations of these complications range from epithelial desquamation to erosion of the cuff through the tracheal wall. These injuries are caused by a combination of the materials employed and the forces exerted by the cuff on the tracheal tissues. The abrasive action of the cuff shears cells from the lining, epithelium adhering to the cuff is removed during extubation, and normal forces exerted on the basement tissues disrupt the blood supply and cause pressure necrosis. These injuries tend to become more severe with increased cuff pressure and duration of ventilation. The first areas affected are generally those of the mucosal membrane, since these are in intimate contact with the device. As these injuries occur deeper they become more serious and begin to affect the blood supply, the cartilage rings, and even the surrounding tissues.

1.2.2 Idealized Models

The most elementary model of tracheal intubation assumes a cylindrical cuff placed statically in a cylindrical tracheal lumen. This is a poor model however, because the trachea cannot be characterized as either cylindrical or static. In reality, the human trachea may exhibit an unlimited variety of cross-sectional shapes including collapsed-circular,

ellipsoidal, or even triangular.[10] The ability of conventional airway devices to conform to any of these shapes is very limited. Furthermore, because the cuffs on these devices have such well-defined profiles the non-ideal tracheal lumen is essentially forced to conform to the shape of the cuff. This ultimately creates stress concentrations in the tissues that result in injury, especially at elevated airway pressures. The seriousness of these injuries is often determined by the deviation of the real cross-section from the ideal.

Clinicians often ignore the state of the airway after seal is achieved. This is dangerous because the trachea elongates, contracts, dilates, and expands during ventilation. Unfortunately, conventional cuff designs cannot maintain seal under these conditions without exerting excessive pressure on the tracheal tissues. In fact, to accommodate the expansion of the tracheal lumen the cuff must essentially be over-inflated. Once the cuff is in this state the trachea may dilate further, requiring additional cuff inflation to maintain seal. This series of events may continually repeat, leading to a condition in which the trachea is stretched to the elastic limits of the tissue. This situation could be corrected by employing a cuff that is flexible enough to conform to the shape of the lumen without stressing the tissues.

In addition to the movement of the trachea, both rotational and translational relative motion occur between the cuff and tracheal lining during ventilation. Because common cuff materials are abrasive this may result in an abrasive action or 'sanding' effect which damages the lining. The potential for serious injury is significant, especially at higher airway pressures and during extended intubation. This severity of the injury may be reduced by employing less abrasive materials and reducing the pressure applied to the trachea. However, this problem has not yet been addressed by industry or academia.

1.2.3 Injury to the Lining

Damage to the tracheal lining is related to deficiencies in both cuff design and material. Almost all endotracheal tube cuffs are constructed from PVC, which is relatively hydrophobic. This type of material is water resistant and generally tends to promote cellular adhesion once contact is made. In practice, a limited amount of pressure is often sufficient to penetrate the mucosal barrier and bring the cuff into direct contact with the tracheal lining. Once this occurs epithelial cells in the lining will often adhere to the cuff, especially if subjected to previous irritation. Relative motion may then forcibly remove these cells from the tissue bed during ventilation. Any adherent cells which survive this procedure will probably be removed during extubation.

The surfaces of many commercially available endotracheal tubes have been shown to be contaminated with abrasive particulate matter. Commercially available vinyl cuffs are not only relatively abrasive to touch but also microscopically rough as evidenced by SEM and AFM microscopy.[11] This type of surface can easily damage the fragile tracheal tissues through the relative motion that occurs during ventilation. Even in the absence of adhesion phenomenon, the combination of particulate contamination and surface roughness is capable of causing injury by abrasive action (sanding effect). Cells previously irritated by adhesion are particularly vulnerable to further injury by this mechanism. When these distressed cells are removed from the lining a gap is left in the tissue bed.

Injury to the mucosa is irreversible because the new growth that occurs during recovery is in the form of squamous, not ciliated epithelium.[12] In fact, if the injury is significant the post-recovery lining may exhibit an absence of both goblet and ciliated cells.

This is important for two reasons. First, even limited destruction of the ciliated epithelium will compromise mucociliary transport. If enough of the lining is destroyed foreign matter will begin to accumulate in the lungs, an unhealthy condition which results in labored breathing, requires constant evacuation, and encourages infection.[5] Next, the tracheal lining is already in an irritated state due to the abrasive action of the cuff. In this condition the lining is vulnerable and may provide a pathway for microbial invasion. Since endotracheal tubes may be contaminated with bacteria by handling, this situation increases the possibility of infection. Even in healthy patients this may lead to serious illness, but in elderly or immuno-compromised patients it may prove fatal.

1.2.4 Injury to the Basement

Even relatively mild cuff pressures may damage the lining. These injuries are serious primarily because they compromise mucociliary transport and lead to infection. Increased pressures and prolonged intubations are even more serious because in addition to destroying the mucosa, the deeper basement tissues and superstructure are affected. It has been estimated that a pressure equivalent to 10 mm Hg is sufficient to impede blood flow to the tracheal tissues, and that any duration of intubation will lead to some level of permanent damage.[3,12] If the blood supply to these tissues is interrupted for extended periods then tissue sloughing or pressure necrosis may result. The soft fatty tissue overlying the cartilage rings is particularly vulnerable because this tends to get compressed between the cuff and the more rigid cartilage. When the cuff pressure is relatively low the tissue between the rings may partially escape compression, but in the region of the cartilage the compression is more

severe and the blood flow is likely to be impaired. Electron photomicrographs invariably reveal the greatest injury in this region, but if blood flow is effectively restricted even the surrounding tissues may be affected.

1.2.5 Injury to the Superstructure

Situations requiring extended intubations at high inflation pressures are not uncommon. Blunt trauma to the airway or lungs may occur in a car accident, fluid accumulation in the lungs is common in drowning victims, and elderly patients may have stiff lungs due simply to age or infirmity. Each of these scenarios represents a low-compliance condition that will require elevated airway pressure during ventilation. For some of these patients the tracheal lining has been previously compromised, so one important consideration is the prevention of scarring. This is nearly impossible of course, because the high cuff pressures required to seal and maintain the airway under these conditions will invariably restrict blood flow and lead to some necrosis. Furthermore, when deeper tissues are damaged the fibrous tissue that develops during recovery may partially occlude the trachea, forming a stenotic area which increases airway resistance and requires surgical correction.[13] In extended duration and high-pressure intubations the cuff has even been known to erode completely through the tracheal wall. The cuff may then breach the carotid artery, the esophagus, or even the external surface of the throat.

1.3 Possible Solutions

1.3.1 Significance

Evidence that these complications are widely recognized is demonstrated in the number of solutions that have been presented by industry and academia. A variety of ideas have been suggested, including revised cuff designs, new materials, and exotic surface treatments. In addition, at least one radically different tube design has been offered. Each of these attempts to address one or more of the previously discussed complications, but for several reasons only a small portion of these ideas have been adopted by industry. Endotracheal tubes have commodity status, so high cost is cited as a key factor in many cases. However, failure to demonstrate a measurable improvement in performance has prevented most of these devices from achieving widespread acceptance.

1.3.2 Cuff Designs

Many new endotracheal tubes designed to reduce the forces exerted on the lumen have been proposed in the patent and technical literature, most of them involving an increase in the length of the cuff. This strategy expands the area over which the sealing pressure is distributed, thereby reducing applied CT forces. Several variations on this theme have been suggested, including multiple cuffs, dual-walled cuffs, longer cylindrical cuffs, and foam-filled cuffs.[14,15,16] The most recent innovation adopted by industry, the 'square' cuff, was implemented more than twenty years ago.[17]

1.3.3 Alternative Materials

A limited number of alternative materials are available on the market. Tubes manufactured from natural rubber, silicone rubber, polyurethane, and even polyethylene are available. Natural rubber tubes are being phased out, while polyurethane is available as a special order item. Silicone rubber tubes are available in commercial quantities, but are not in widespread use. The highly biocompatible and smooth surface presented by silicone should translate into fewer problems with abrasion and cellular adhesions. However, these tubes often suffer from irregular cuff profiles, are prone to leaks, and square cuffs are not available. Silicone tubes are also much more expensive than conventional tubes.

1.3.4 Surface Treatments

Several hydrophilic coatings applied by spray-coating, dip-coating, or graft polymerization are mentioned in the patent literature.[18,19,20] Some of these are applied by the manufacturer, while some are designed to be applied by the end-user to existing medical devices. These coatings improve performance by apposing a highly wettable surface to the target tissue. This idea has been employed effectively on a variety of medical devices, including surgical tools, guidewires, catheters, contact lenses, and ocular implants. Still, these coating processes often suffer from poor durability and inadequate coating thickness. These processes also add considerable expense to the end product.

1.3.5 New Technologies

An entirely new tube design employing a series of 'ultra-thin gills' in place of the traditional cuff was recently proposed by scientists at the National Institutes of Health.[21] This device is constructed from nickel-alloy reinforced polyurethane and is designed to be placed into the airway so that the gills 'straddle' the vocal cords, sealing the airway at that location. In theory this should prevent damage to the mucosal lining by maintaining the seal external to the trachea in the region of the vocal cords. However, independent testing on this device has not been performed. Possible drawbacks include poor seal at low-compliance, inadequate airway security, vocal cord irritation, high production costs, and increased training costs.

1.4 Hydrogel Devices

The complications associated with tracheal intubation may be reduced or eliminated by employing an airway device constructed from hydrogel materials. Hydrogels are a class of crosslinked polymers that swell in the presence of moisture and may contain more than 95% water by weight. Swelled hydrogels are ideal for many medical applications because they are soft and tissue-like, with smooth, lubricious, non-abrasive surfaces. By placing these materials in apposition to the tracheal lining it should be possible to reduce the incidence of injury associated with abrasion, friction, pressure, and cellular adhesion.

Hydrogel materials attract a boundary layer of water in aqueous environments. This begins to form at the onset of swelling and causes the polymer material at the surface to become partially solvated. The free chain ends that reside in this layer probably resemble a 'sea of wheat' and impart a slippery feel to the surface. This 'surface in solution' not only

increases the separation distance between the hydrogel and the host tissue but also serves as a lubricating agent to reduce friction with contacting surfaces. This is an especially valuable combination of attributes for devices that experience relative motion with soft tissues and should help to reduce the incidence of injury associated with friction and abrasion.

In the swelled state hydrogel materials exhibit highly wettable surfaces. This is an important consideration in the fabrication of medical devices because wetting surfaces tend to resist cellular adhesion and bacterial colonization more effectively than non-wetting surfaces. Airway devices employing hydrogel materials should therefore reduce the incidence of adhesive injury by leaving cells in the tissue bed rather than affixed to the device. As previously stated, this type of injury is dangerous because breaches in the tissue bed provide a pathway for bacterial invasion. Hydrogel airway devices should diminish the threat of secondary infection by reducing the incidence of adhesion phenomenon.

Hydrogels are generally flexible in the hydrated state. The mechanical performance of these materials depends on the degree of swelling, but in general they tend to transform from rigid glass to flexible elastomer as the water content increases. The exceptional flexibility that develops in the higher water content gels will often allow extensive deformation prior to failure. Endotracheal tube cuffs fabricated from these materials should easily conform to the convoluted shape of the tracheal lumen. This would allow the cuff to more evenly distribute the sealing pressure without creating the severe stress concentrations that characterize more conventional cuffs. Furthermore, since hydrogel materials increase in both mass and size during swelling, the possibility exists that volume swelling could be employed to assist in maintaining the seal. This strategy would reduce local applied forces

by distributing the seal over the entire length of the device. This in turn should help to reduce injuries associated with high applied CT pressure, particularly in the region of the cartilage rings where cuff compression is more severe.

1.5 Summary

Endotracheal intubation involves the placement of a tube into the tracheal lumen, and is prescribed in any setting in which the airway must be stabilized or the patient anesthetized. The purpose of the endotracheal tube in these procedures is to maintain a viable airway, facilitate mechanical ventilation, allow the administration of anesthetics, and prevent the reflux of vomitus into the lungs. In order to satisfy these requirements a nearly airtight seal must be maintained between the tube and the tracheal lining. Most conventional endotracheal tubes provide this seal by employing a cuff that is inflated once the tube is in place. However, the design of this cuff and surface properties of the material are often a source of irritation and injury to the tracheal tissues. In fact, the complication rate for endotracheal intubation is reported to be between 10 and 60%, with manifestations ranging from severe sore throat to erosion through the tracheal wall. These complications are caused by a combination of the materials employed and the forces exerted by the cuff on the tracheal tissues. In particular, the abrasive action of the cuff shears cells from the lining, epithelium adhering to the cuff is removed during extubation, and normal forces exerted on the basement tissues disrupt the blood supply and cause pressure necrosis.

The complications associated with tracheal intubation may be reduced or eliminated by employing airway devices constructed from hydrogel materials. Hydrogels are a class of

crosslinked polymers which swell in the presence of moisture, and may contain more than 95% water by weight. Hydrogels are ideal for this application because they are soft and tissue-like, with smooth, lubricous, and non-abrasive surfaces. By placing these materials in apposition to the tracheal lining many of the injuries associated with abrasion, friction, pressure, and cellular adhesion could be significantly affected. First, an increase in lubricity should reduce the incidence of injury associated with friction and abrasion. Next, a reduction in cellular adhesion should diminish the threat of secondary infection by maintaining the integrity of the tracheal lining. Finally, by employing volume swelling to assist with sealing, a reduction in pressure-related injuries should be realized, especially in the region of the cartilage rings where cuff compression is more severe.

CHAPTER 2
HYDROGEL POLYMERS

2.1 Introduction

2.1.1 Definition

Hydrogels are traditionally defined as crosslinked polymers which swell in the presence of moisture. This definition may be expanded for this document to include any polymeric material which swells in aqueous media without dissolving near physiologic temperature (37°C). The physical properties of these gels are highly dependent on water content, which is affected by processing, chemical composition, and crosslinking. These materials are typically mechanically weak, but also feature smooth, lubricious, non-abrasive surfaces. In spite of poor mechanical strength these materials often find use in medical applications, primarily because of advantageous surface characteristics.

2.1.2 Bonding

Hydrogels belong to a class of polymers with a natural affinity for water. This attraction may be attributed to the hydrophilic nature of pendent groups on the main chain. The presence of these substituents (OH, COOH, NH_2, $CONH_2$, etc.) causes strong polar bonds to develop between the solvent (water) and the polymer. These bonds may be

described as dispersive because they act to separate the chains and dissolve the gel. However, these same pendent groups are also responsible for strong cohesive bonds. Inter-chain forces attributed to dipole interaction or hydrogen bonding hinder dissolution because they tend to bring the chains together. The relative strength of these two opposing forces depends on the density and composition of the substituents. The dispersive force is normally stronger, so the natural tendency is for the hydrogel to dissolve, but if an equilibrium between the dispersive and cohesive forces is attained the gel may remain viable.

2.1.3 Crosslinking

The distinction between hydrophilic polymer and hydrogel depends primarily on solubility. Both material types will swell in the presence of moisture to some equilibrium value, but hydrogels will retain their shape without dissolving. Cohesive forces provide some resistance to dissolution, but in general this is prevented by crosslinking. These crosslinks prevent dissolution by restricting chain mobility and may be chemical or physical in nature. Chemical crosslinks are created by covalent or ionic bonding between the chains, while physical crosslinks are provided by the presence of crystallinity or other entanglements. Both types are equally effective at transforming the polymer mass into an insoluble three-dimensional network, essentially creating one enormous molecule. Chemical crosslinks are irreversible so the resulting polymer is a thermoset, while physical crosslinks are thermally labile and result in a thermoplastic. Chemically and physically crosslinked hydrogels are known as chemical and physical gels, respectively. The density and nature of the crosslinks have a profound influence on both bulk and surface properties.

2.1.4 Chain Mobility

Hydrogel materials begin to swell when water molecules pass between adjacent chains and separate them. This occurs because the mobility of the water molecule allows it to closely approach and associate with the hydrophilic pendent groups. The presence of these water molecules in the network increases free volume, enhancing segment mobility and allowing a significant increase in rotational and translational flexibility at the molecular level. In effect, these water molecules reduce the glass transition temperature of the hydrogel.

Chain mobility is largely responsible for both the flexible nature and poor mechanical strength exhibited by most hydrogels. Decreasing chain mobility by increasing the molecular weight or crosslink density will improve strength, but will also decrease flexibility and limit swelling. Careful consideration must be given to changes in the chemical or physical nature of the gel because an improvement in one property may be offset by deterioration in another. In practice, each application presents a unique set of material requirements, but an acceptable balance between swelling performance and mechanical properties may often be achieved with moderate molecular weight and light crosslinking.

2.1.5 Pore Structure

Most hydrogel materials are porous to some extent. Pore structure has a profound effect on overall hydrogel performance because it affects the amount of retained water and transport through the material. Highly porous gels absorb water more quickly, swell to a greater extent, and pass solute particles at an increased rate. Porosity also tends to enhance flexibility and reduce strength. The development of pore structure is highly dependent on

processing parameters, especially the amount of water present in the casting solution and the solubility of the polymer in the monomer. Hydrogels are generally classified as nonporous, microporous, or macroporous depending on pore size and distribution.[22]

Polymers with significant solubility in the monomer will normally result in nonporous hydrogels. These gels form in a nonporous conformation because the polymer remains in solution with the monomer during polymerization. This prevents the inclusion of imperfections (pores) in the network that might otherwise form due to phase separation. The absence of porosity causes the water content to be dictated exclusively by the chemical structure and degree of crosslinking of the gel and results in a lower water content than in comparable porous gels. The lower water content also causes these materials to exhibit decreased flexibility, increased density, and greater strength relative to porous gels.

Polymers with fair solubility in the monomer will normally result in microporous hydrogels. In this case the network forms in a porous conformation because phase separation occurs between the polymer and monomer during polymerization. This allows the development of imperfections in the network that are manifested by porosity. The resulting systems are relatively homogeneous, with pore sizes ranging from 50 to 200 Angstroms.[22] The internal volume provided by this pore structure increases the swelling capacity of the material beyond the values attained by comparable nonporous gels. The moderate degree of swelling also allows these materials to strong and flexible.

Polymers that are insoluble in the monomer will normally result in macroporous hydrogels. Phase separation during polymerization is pronounced for these materials so very large (0.1 μm) voids tend to develop.[22] These voids are incorporated into a highly irregular

surface that gives the gel a sponge-like appearance. This type of gel is characterized by high water content and excellent wettability due to the presence of large pockets of water at the surface. These unique surface characteristics make macroporous gels attractive for many medical applications, particularly those involving cellular ingrowth. Unfortunately, the strength and flexibility of these materials are generally very limited.

Porosity is not normally maintained intact in the dry state. The pore structure will tend to collapse to varying degrees during desiccation, depending on the rate of drying. Slow dehydration will generally allow the pores to collapse, while faster dehydration will better preserve the natural pore structure. Simple methods such as air or oven drying result in shallow dehydration curves that tend to collapse the pore structure. Gels desiccated by these methods are termed xerogels. In order to better preserve the pore structure the water may be frozen prior to extraction. This prevents translation of the polymer network while the water is being removed. Common techniques for removing solid water from gels include freeze drying and critical point drying. Freeze drying removes the water by sublimation while critical point drying involves extraction by solvent exchange with a supercritical fluid (often CO_2). Gels desiccated by either of these methods are termed aerogels.

2.1.6 Water Structure

Water in swelled hydrogels may be classified as either pore water or bound water. Pore water is highly mobile and is responsible for most of the diffusion and solute transport through the gel. Since these pores do not entirely collapse in the dry state, a relatively large amount of pore water may be transferred to or from the gel before a significant change in

volume occurs. Water in the pore structure does not plasticize the polymer chains and has no direct effect on flexibility. Pore water is also known as freezing water because it is physically unconstrained and free to undergo a phase change at the freezing point.

Bound water hydrates the hydrogel at the molecular level, clustering around the hydrophilic pendent groups on the main chain. These molecules are responsible for creating the dispersive forces which separate the polymer chains and increase free volume. The addition of these molecules also provides much of the volume change that occurs during swelling. In this capacity the bound water plasticizes the polymer chains and is partially responsible for the flexible nature of the gel. When water is extracted from the gel during desiccation the pore water is always removed first. The ratio of bound water to pore water in the hydrogel depends on chemical composition and processing.

2.2 Properties

2.2.1 Hydrophilicity

Hydrophilicity is a property which describes the ability of a polymer to absorb water. The main measure of hydrophilicity is equilibrium water content (EWC), the mass percentage of water in the polymer at the equilibrium swelling point. The EWC is determined with [2.1], where M_w and M_d are the wet mass and dry mass of the gel sample, respectively.

$$EWC = (M_w - M_d) / M_w \qquad [2.1]$$

respectively. It is important to determine M_w at the expected operating temperature of the material because this value often varies considerably. This calculation may be employed at either room temperature or physiologic temperature.

2.2.2 Wettability

Wettability may be defined qualitatively as the tendency of liquid to spread over and adhere to a surface. Naturally, when this definition is applied to hydrogel materials the liquid in question is water. Water tends to spread easily on hydrogel surfaces so by definition these materials are described as both hydrophilic and wettable. Conversely, water beads on more hydrophobic materials such as polyvinyl chloride (PVC) or polypropylene (PP), so these are generally described as non-wettable.

Wettability and hydrophilicity are related terms that are often confused and sometimes used interchangeably. In reality, wettability and hydrophilicity are surface and bulk properties, respectively that have different origins. A hydrogel will normally be both hydrophilic and highly wetting because the material is generally chemically identical (homogeneous) in the bulk and at the surface. Hydrophobic materials are described as having non-wetting surfaces for similar reasons. The only exception to this rule occurs in the case of surface-modified or coated materials. For example, a hydrophobic medical device such as an intravenous catheter may be coated with a hydrogel to improve biocompatibility. This modified device may still be considered hydrophobic because the bulk material absorbs a negligible amount of water. The surface, on the other hand exhibits wetting behavior due to the presence of the gel layer. Of course, this distinction is largely academic because only the surface of the device comes into contact with the host tissue. Still, some scientists feel that hydrophilicity is not sufficient to characterize hydrogel surfaces and instead prefer to rely on measurements of wettability. Common techniques available to quantify wettability include critical surface tension of the solid and the measurement of contact angle.

2.2.3 Contact Angle

Consider the droplet in Figure 2.1, where the liquid forms an angle θ with the solid surface. According to Young, the surface tension of the solid in contact with air is γ_{sv}, with a corresponding surface area of A_{sv}.[23] The surface tension of the liquid in contact with air is γ_{lv}, with a corresponding surface area of A_{lv}. The interfacial tension between the solid and liquid is γ_{sl}, with a corresponding contact area of A_{sl}. The natural tendency of the droplet in equilibrium is to minimize free energy (G):

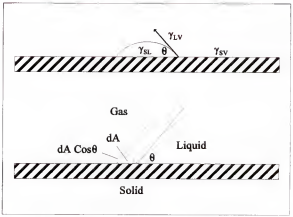

Figure 2.1 Contact angle created by a droplet on a solid surface. This contact angle is affected not only by surface tension, but also temperature, viscosity, contamination, and other interface characteristics.

$$G = \gamma_{sv} A_{sv} + \gamma_{lv} A_{lv} + \gamma_{sl} A_{sl} \qquad [2.2]$$

If this droplet spreads an infinitesimal amount so that the interfacial area increases by dA, then there is a corresponding decrease in A_{sv} and increase in A_{lv}. Assuming that the change in A_{lv} is equal to dAcosθ and substituting these values in [2.2] yields

$$dG = \gamma_{sl}\, dA + \gamma_{lv}\, dA\cos\theta - \gamma_{sv}\, dA \qquad [2.3]$$

However, dG is essentially zero because the droplet is in equilibrium. This leads to Young's equation relating surface tension and contact angle:

$$\cos\theta = (\gamma_{sl} + \gamma_{sv}) / \gamma_{lv} \qquad [2.4]$$

It may be seen from [2.4] that wettability is related to a localized field of attraction emanating from both the surface and the associated liquid. This relation may be used to calculate the expected contact angle if the appropriate surface tension values are known. It should be

recognized however, that this treatment only provides an estimate of wettability and that quantitative predictions must be viewed with caution. In practice, wettability and contact angle depend on many factors other than surface tension, including contamination at the interface, viscosity, temperature, and surface homogeneity. In any case, a quick contact angle measurement will provide a good indication of surface wettability. Surfaces are generally described as reasonably wettable when exhibiting contact angles less than 60°, and fully wettable when exhibiting contact angles less than 10°.[24]

2.3 Performance

Hydrogels become softer and more flexible as the water content increases. Mechanical properties depend to a large extent on the degree of swelling, but in general hydrogels transform from rigid glass to flexible elastomer as the degree of swelling increases. The exceptional flexibility that develops allows these materials to experience extensive deformation without failure, and devices fabricated from these materials can often conform to convoluted shapes. However, the advantageous surface properties of these gels are associated with the swollen state. Since there is an inverse relationship between strength and water content these gels must often be employed in combination with other materials.

Typical hydrogels contain between 25 and 95% water by weight in the fully hydrated state. When these gels are placed in an aqueous environment the surface attracts a boundary layer of water and begins to exhibit a 'slippery' feel. This occurs because the polymer at the surface swells and becomes partially solvated in the fluid layer. The polymer chains at the surface drift in this fluid layer and essentially form a viscous solution. This boundary layer

serves to increase the separation distance between the hydrogel and contact area and has a lubricating effect on the interface. These are especially valuable attributes for medical devices that must endure sliding contact or relative motion with living tissues. By increasing the separation distance and enhancing lubrication, medical devices fabricated from hydrogel materials should cause fewer abrasive injuries.

Hydrogels are also much more wettable than most materials, a feature which generally reduces the tendency of a surface to experience cellular adhesion or bacterial colonization in aqueous environments. This is important when considering materials for the fabrication of tissue contact devices. Cells that remain fixed in the tissue bed are less likely to suffer injury than those that adhere to a medical device, particularly if relative motion is involved. Cells that are damaged by the device leave a gap in the tissue bed that provides a pathway for bacterial invasion. Since medical devices are often contaminated by handling, these injuries increase the possibility of contracting infection. Devices fabricated from these materials should help to eliminate this threat by reducing adhesive injuries.

2.4 Applications

In spite of what are often viewed as inadequate mechanical properties, hydrogel materials are employed in a wide variety of medical applications. For example, these materials find use in controlled drug release, surgical adhesion barriers, soft contact lenses, wound dressings, surgical sponges, and many other applications. Hydrogels may be employed in sheet or particulate form, applied to a surface as a coating, or fashioned into a device. These materials are normally selected for medical applications because of their

unique surface properties and general compatibility with living tissues. Hydrogel materials are employed in these applications because the highly lubricious and wettable surfaces reduce the incidence of injury associated with friction, abrasion, and cellular adhesion.

A team of scientists at the University of Florida is currently investigating the possibility of employing hydrogel materials in the manufacture of airway devices. Hydrogel materials are ideal for this application because they are soft and tissue-like, with smooth, lubricious, non-abrasive surfaces. By placing these materials in apposition to the tracheal lining many of the injuries associated with pressure, friction, abrasion, and cellular adhesion could be reduced or eliminated. However, many questions about material properties and manufacturing difficulties must first be answered. If these problems prove manageable it is possible that these devices could revolutionize airway maintenance.

2.5 Fabrication

2.5.1 Selection Criteria

The hydrogels selected for use in this study will ultimately be employed in endotracheal tubes and other soft tissue contact devices. To prove useful in these applications these materials must possess all of the unique surface properties that have been discussed in previous sections. Hydrogels with high water content are generally preferred because this tends to enhance flexibility, wettability, and swelling performance. When designing these materials however, a balance must be sought between surface properties, which improve with increased water content, and mechanical strength, which degrades. Ideal materials exhibit superior wettability, smoothness, and lubricity, great strength, and exceptional elongation

while minimizing modulus (strong, but soft materials). In pursuing this ideal many candidate materials were evaluated in the laboratory on the basis of mechanical properties such as tensile strength, modulus, elongation, and resistance to creep. Consideration was also given to equilibrium water content, swelling kinetics, and surface finish.

After thoroughly reviewing the scientific literature and conducting extensive laboratory tests and observations, performance criteria of 25 psi (minimum) tensile strength, 20 psi (maximum) modulus, 50% (minimum) EWC, and 300% (minimum) ultimate elongation were defined for all hydrogel materials. The first of these, the strength criterion was based on the mechanical modeling (Chapter 6) of several gel formulations. During these trials it was discovered that a tensile strength of 25 psi was sufficient to survive an extended simulated intubation. Next, the elongation criterion was based on an estimate of the expected deformation assuming a low-profile hydrogel cuff was inflated under actual use conditions. Studies later proved that this value was unnecessarily restrictive when materials with elongation values below 300% performed adequately in mechanical simulations. Finally, the EWC criterion was prescribed as 50% because subjective evaluations of the surfaces led to a belief that this represented an approximate lower limit for the exhibition of lubricious behavior. It is important to note, however that these criteria were identified in the initial stages of the materials search, and as such served only as a guide and point of reference for second generation materials. In reality, the nominal values of strength, modulus, elongation, and water content required for acceptable performance in real world situations have yet to be determined. Still, several candidate hydrogel materials (Table 2.1) satisfied these selection criteria and were shown to perform well in mechanical simulations.

Table 2.1 Hydrogel materials which satisfy the selection criteria include 2-hydroxyethyl methacrylate (HEMA), methyl methacrylate (MMA), n-vinyl pyrrolidone (NVP), lauryl methacrylate (LMA), poly(vinyl alcohol) (PVA), and poly(vinyl pyrrolidone) (PVP).

Designation	Material Description
HR	Solution polymerized poly(HEMA) hydrogel
HM85F	Bulk polymerized HEMA-MMA copolymer
HN4030G	Solution polymerized HEMA-NVP copolymer
HNM4020G	Solution polymerized HEMA-NVP-MMA terpolymer
HNL4020G	Solution polymerized HEMA-NVP-LMA terpolymer
IPN	HEMA-PVP interpenetrating polymer network
PVA	PVA gelled from 8% solution in mixed solvent
FT-PVA	PVA precipitated from 8% solution by freezing

2.5.2 HEMA-Based Hydrogels

Poly(2-hydroxyethyl methacrylate) is probably the most studied hydrogel in the medical device industry. Virtually every author who has written on the subject since 1960 mentions the landmark paper by Wichterle, in which poly(HEMA) is first described as a potentially useful material for the fabrication of contact lenses.[25] The unique properties of this material are attributed to a repeat unit (Figure 2.2) which exhibits an amphiphilic nature.

This feature is provided by the two substituents on the second carbon atom, a hydrophobic methyl group and a hydrophilic acrylic group. The swelling capacity of the gel is accounted for by the polar nature of the carbonyl and hydroxyl functionality on the acrylic group. The flexible nature of the gel results from a combination of chain mobility and free volume. The chain is constructed from carbon-carbon single bonds, which enhance flexibility by allowing relatively free rotation along the entire length of the chain. The large acrylic groups increase free volume by separating the polymer chains from one another. These features partially account for the flexibility of the swollen gel.

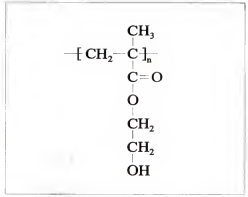

Figure 2.2 The repeat unit of poly(2-hydroxyethyl methacrylate).

Poly(HEMA) hydrogels may be fabricated by bulk, solution, emulsion, or suspension polymerization. However, the author typically forms these materials by casting in solution with a divinyl crosslinking agent. This method helps to prevent residual stresses in the finished product by polymerizing the gel in the swelled state. The associated free-radical polymerization reactions are normally initiated with a thermal decomposition agent such as azobisisobutyronitrile (AIBN) or benzoyl peroxide, but ultraviolet and visible light initiators, as well as gamma or electron beam radiation are also employed. The properties of the end product may be modified by adjusting the casting water content, the degree of crosslinking, or by copolymerization with other monomers.

The casting water content refers to the mass percentage of water in the syrup, while the syrup is defined as the combination of water, monomer, initiator, and any other additives

in the casting prior to polymerization. If the casting water content is lower than the EWC of the end product (approximately 35%) the resulting hydrogel is normally homogeneous, relatively nonporous, and optically transparent. As the casting water exceeds the EWC (from 40 to 50%) the gel begins to phase separate during polymerization, becoming increasingly microporous and translucent. This structure causes the material to exhibit superior flexibility and wettability compared to the comparable nonporous gel, but tensile strength is also slightly reduced. Poly(HEMA) hydrogels fabricated with a casting water content from 50% to 60% exhibit a macroporous structure. These gels are highly wettable but are opaque and very weak. If the casting water content exceeds 60% no gel will form.

The mechanical strength of these gels may be enhanced by increasing the degree of crosslinking. In practice this may be accomplished by increasing the amount of crosslinking agent added to the syrup. This reduces the molecular weight between crosslinks and decreases chain mobility. Unfortunately this also reduces flexibility and the ultimate degree of swelling. Because unmodified poly(HEMA) hydrogels have a fairly low EWC to begin with (about 35%) the degree of crosslinking should be kept to a minimum. Excessive crosslinking has a negative impact on wettability and also embrittles the gel.

Both the mechanical properties and surface characteristics of poly(HEMA) hydrogels may be modified by the addition of complementing monomers to the syrup. These monomers may possess either hydrophobic or hydrophilic character. The addition of a hydrophobic monomer such as methyl methacrylate (MMA) or lauryl methacrylate (LMA) generally has the same effect on properties as increasing the degree of crosslinking. The resulting copolymer generally exhibits reduced swelling, wettability, and elastic performance while

tensile strength is improved. Applications for these materials are somewhat limited because they tend to exhibit poor wettability (for a hydrogel). Conversely, the addition of a hydrophilic monomer such as n-vinyl pyrrolidone (NVP) or methacrylic acid (MA) improves flexibility, wettability, and swelling performance while reducing mechanical strength. As always care must be exercised when formulating the gel to gain proper balance between mechanical properties and surface characteristics. Some situations may require multiple monomers employed in combination to tailor properties to a specific application. However, results may be unpredictable due to variations in reactivity ratios among different monomers. The following passages describe the processes that were employed for polymerizing poly(HEMA) hydrogels and other HEMA-based copolymers and terpolymers for these studies. All of these processes employed distilled or purified reagents as appropriate. Mixed syrups were degassed and refrigerated under argon for later use.

Poly(HEMA) hydrogels. These gels are cast in various glass vessels from an aqueous solution containing 65% Kodak HEMA monomer and 35% distilled water. The polymerization is carried out using a 0.5% sodium bisulfite - ammonium persulfate redox initiation system. The initiator is measured out and dissolved in the water component by swirling for several seconds. The monomer is then added to this solution while mixing on a stirplate. After stirring for ten minutes the solution may be poured into the molds. Unlike most syrups, these solutions are difficult to store because the initiator decomposes below room temperature. Also, since the decomposition of the initiator is exothermic a significant amount of heat is evolved. To prevent autoacceleration and bubble formation the castings must be chilled in a water bath during polymerization.

HEMA-MMA copolymer. These gels are cast in various glass vessels from a solution containing 85% Kodak HEMA monomer and 15% Aldrich MMA (Figure 2.3) monomer. Polymerization is carried out using 0.5% AIBN initiator. The initiator is measured out and dissolved in the MMA by mixing on a stirplate for ten minutes. After the initiator dissolves the HEMA monomer is added and the solution is stirred for an additional 20 minutes. The resulting syrup may be cast immediately by immersion in a water bath at 45°C or refrigerated under argon for later use.

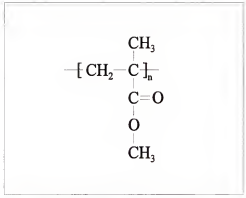

Figure 2.3 The repeat unit of poly(methyl methacrylate).

HEMA-NVP copolymer. These gels are cast in glass vessels from a solution containing 40% Kodak HEMA monomer, 30% Aldrich NVP monomer (Figure 2.4), and 30% distilled water. The components are measured out and poured together into a flask which is mixed on a stirplate for thirty minutes. After degassing the resulting syrup may be stored in the refrigerator under argon or polymerized by subjecting the casting to a 35 krad dose of gamma radiation at 25°C over an 8 hour period.

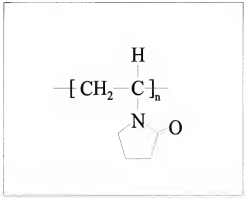

Figure 2.4 The repeat unit of poly(n-vinyl pyrrolidone).

HEMA-NVP-MMA terpolymer. These gels are cast in various glass vessels from a solution containing 40% Kodak HEMA monomer, 20% Aldrich NVP monomer, 10% Aldrich MMA monomer, and 30% distilled water. The components are measured out and

poured together into a flask which is mixed on a stirplate for thirty minutes. The syrup may be degassed and stored in the refrigerator under argon or polymerized by subjecting the casting to a 25 krad dose of gamma radiation at 25°C over a 6 hour period.

HEMA-NVP-LMA terpolymer. These gels are cast in various glass vessels from a solution of 40% Kodak HEMA monomer, 20% Aldrich NVP monomer, 10% Kodak LMA monomer (Figure 2.5), and 30% distilled water. The components are measured out and poured together into a flask which is mixed on a stirplate for thirty minutes. The syrup may then be degassed and refrigerated under argon, or polymerized by subjecting the casting to a 25 krad dose of gamma radiation at 25°C over a 6 hour period. The resulting terpolymer has a tendency to adhere to the glass mold so these must frequently be broken to remove the casting. This is usually simplified by cracking the mold and soaking in warm water for several hours.

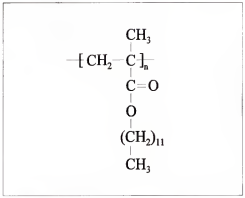

Figure 2.5 The repeat unit of poly(lauryl methacrylate).

2.5.3 HEMA-PVP IPN Hydrogels

Interpenetrating polymer networks (IPN) are normally defined as a combination of two or more intermingled polymers that are polymerized and crosslinked independently. Semi-interpenetrating polymer networks (SIPN) are similarly defined as IPN materials in which only one of the polymers is crosslinked. Both definitions are somewhat lacking because in practice crosslinking is not always necessary or even beneficial. In fact, in some

cases crosslinking may actually prevent the development of desired properties. The formation of domains or entanglements is often sufficient to render the material insoluble at normal operating temperatures so crosslinking agents may often be omitted from the syrup. For the purpose of this document a single unified definition of IPN materials will be followed. This definition specifies only that the IPN material is composed of two or more polymeric species that are independently polymerized.

IPN systems may be employed to enhance the properties of the 'base' hydrogel. The second component may improve the strength, flexibility, or wettability of the hydrogel depending on the concentration and chemical characteristics of the added material. In this study the addition of PVP polymer to the base poly(HEMA) hydrogel serves to increase water content, greatly improving the wettability and flexibility of the resulting material. As with other hydrogels the properties of these IPN materials may be adjusted by modifying the degree of crosslinking or the casting water concentration. However, the largest variations in performance are realized by adjusting the concentration and molecular weight of the PVP polymer phase. The IPN gels employed in this study are fabricated by solution polymerizing Fluka HEMA monomer in the presence of Aldrich poly(vinyl pyrrolidone) polymer (300,000 M_w). The syrup is a combination of HEMA monomer, PVP polymer, distilled water, and AIBN initiator. Variation in the component ratios is designed to tailor the gel to different applications and several formulations are listed in Table 2.2. The basic fabrication process (Table 2.3) involves combining two solutions, the polymer dissolved in water, and the initiator dissolved in the monomer. After mixing and degassing the resulting syrup may be cast immediately or stored under argon. However, storage at room temperature for extended

periods is safe and perhaps even beneficial. Slow polymerization of the syrup over time at this temperature enhances the molecular weight of the HEMA phase. This tends to improve the strength, flexibility, and durability of the resulting gel.

Table 2.2 Component ratios of interpenetrating polymer network hydrogels fabricated from poly(2-hydroxyethyl methacrylate) and poly(vinyl pyrrolidone).

Designation	Mass Percent of Component			
	HEMA	**PVP**	**Water**	**AIBN**
IPN15	18.0%	12.0%	70%	0.1%
IPN20	20.0%	10.0%	70%	0.1%
IPN25	21.5%	8.5%	70%	0.1%
IPN30	22.5%	7.5%	70%	0.1%
IPN35	23.3%	6.7%	70%	0.1%
IPN40	24.0%	6.0%	70%	0.1%
IPN45	24.5%	5.5%	70%	0.1%

Table 2.3 A process tabulation for IPN hydrogel fabrication. Aldrich PVP (300,000 M_w) is used as received. Fluka HEMA monomer (99.5% purity) is double distilled under vacuum. Water is also distilled prior to use. Kodak AIBN initiator is recrystallized from ethanol. Molds are described in detail in chapter 5.

Step	Directions
1	Clean the glass mold surfaces thoroughly with ethanol. After drying assemble the mold on a level surface.
2	Determine the quantities of reagent required. The IPN20 formulation calls for a syrup composed of 10% PVP, 20% HEMA, and 70% water. Each 100 grams of solution requires 10 grams of PVP, 20 grams of HEMA, and 70 grams of water.
3	Flask A. Add the proper amount of water to a round bottom flask and set on a stirring hotplate. Heat the flask to 90°C.
4	Flask B. Mix the monomer and initiator in a round bottom flask. Add an amount of AIBN equal to 0.1% of the monomer mass. Set this flask aside and mix on a stir plate (low setting).
5	Slowly add the PVP polymer to flask A. Solution is encouraged if the polymer is added slowly. Once dissolution is complete remove the heat and continue stirring. Allow the flask to cool to room temperature.
6	Add the contents of flask B to flask A. Stir at room temperature for 6 hours, then hold in vacuum for 15 minutes. The resulting solution may be stored at room temperature under Argon or cast immediately.
7	Charge the mold to the fill line and loosely place the upper O-ring. The ring shall be left in this position during polymerization.
8	Place the charged mold into a heated water bath at 45°C. Maintain this temperature for 1 hour, then increase the temperature by 1°C every hour for 5 hours. Hold the temperature at 50°C for 18 hours, then increase to 60°C. Hold at this temperature for 6 hours.
9	Remove the mold from the bath and cool to room temperature. Break down the mold and remove the casting. Place this in a warm water bath to extract residual initiator and monomer. Once the impurities are removed fabrication is complete.

2.5.4 PVA Hydrogels

Poly(vinyl alcohol) is normally produced by the acid-catalyzed hydrolysis of poly(vinyl acetate), which effectively converts the pendent acetate groups to hydroxyl groups. The properties of the resulting polymer are determined by tacticity, degree of hydrolysis, and molecular weight. Most commercial grades of PVA (Figure 2.6) are stereoregular (primarily isotactic) with less than 2% of the repeat units forming in the 'head-to-head' (adjacent hydroxyl groups) configuration. In theory this should allow a high degree of crystallinity in the finished product. However, this is hindered by the presence of residual acetate groups so the tendency toward crystallization depends primarily on the degree of hydrolysis. This refers to the percentage of converted acetate groups on the main chain. Partially hydrolyzed grades (less than 75% conversion) do not crystallize significantly and are soluble in water at room temperature. This is because the large number of bulky acetate groups increases free volume and prevents the long-range interchain associations required for crystallization to occur. As the degree of hydrolysis increases the loss of bulky acetate groups reduces free volume and the chains are allowed to more closely approach one another. The compact but highly polar hydroxyl groups then come into close proximity and 'bind' the chains together through strong hydrogen bonding. These interchain forces increase the degree of crystallinity and greatly reduce solubility. In fact, in spite of the high concentration of hydroxyl groups completely hydrolyzed grades (greater than 99% conversion) of PVA must

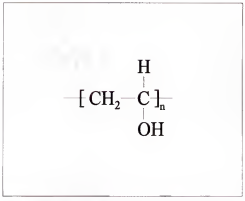

Figure 2.6 The poly(vinyl alcohol) repeat unit. Polymerization is usually head to tail.

be heated to nearly 100ºC to attain solution. These materials exhibit excellent mechanical properties and chemical resistance but can also swell to a significant degree.

The properties of PVA hydrogels vary with molecular weight, but since these materials are normally obtained in polymer form the molecular weight cannot easily be adjusted. Instead these properties are typically modified by means of chemical or physical crosslinking. Chemical gels are easily formed by the addition of agents which undergo condensation with the hydroxyl groups on the main chain. A number of aldehydes (glutaraldehyde, formaldehyde, etc.), dicarboxylic acids (adipic acid, terephthalic acid, etc.), and metal ions (Fe^{3+}, B^{2+}, etc.) will form chemical bonds with PVA which result in crosslinks. Longer molecules such as diacids are generally preferred over metal ions because the ion 'bridge' is short and restrictive, embrittling the material. Molecules such as adipic acid can effectively restrict chain mobility while maintaining some measure of flexibility.

Physical gels are formed by crystallization. The required orientation may be induced by drawing the material, by heat treatment, or by casting the polymer in solution with a gelling agent. These agents create specific interactions between the hydroxyl groups on adjacent chains, bringing them together to improve hydrogel bonding. Many such agents are known, and this process is easily employed on a laboratory scale. This is the method the author employed for the fabrication of PVA gels used in this study. The process (Table 2.4) is very simple and basically only involves dissolving the polymer in a solution of water and the gelling agent, dimethyl sulfoxide (DMSO). This solution will spontaneously gel over several hours at room temperature or when chilled. The properties of the resulting gel depend on the molecular weight and concentration of the polymer in solution, as well as the

concentration of the gelling agent. Increasing the concentration of the agent tends to improve mechanical strength, but also reduces swelling. At any rate, the amount of gelling agent should be minimized because it must be extracted prior to use.

Table 2.4 A process tabulation for standard poly(vinyl alcohol) hydrogel fabrication. Kodak PVA (99% hydrolyzed, 100,000 MW) and Mallinckrodt DMSO (dimethyl sulfoxide) are used as received. Water is distilled prior to use. The resulting syrup may be cast immediately or stored indefinitely at room temperature. Mold design is described in detail in chapter 5.

Step	Directions
1	Clean the appropriate glass mold with ethanol and assemble on a level surface.
2	Determine the quantities of reagent required. An 8% PVA solution will be prepared in a 1:1 mixed solvent. 100 grams of solution will require 8 grams of PVA, 46 grams of DMSO, and 46 grams of water.
3	Create the mixed solvent by adding equal portions of water and DMSO to a round bottom flask. Set the flask on a stirring hotplate and equilibrate to 85°C.
4	Add the PVA polymer to the flask while stirring. Solution is encouraged if the polymer is added slowly. Continue stirring until dissolution is complete.
5	After solution is achieved loosely cap the flask, reduce the temperature to 75°C, and continue stirring for a period of 6 hours. After this time the solution may be stored at room temperature for later use or reheated to 85°C for casting.
6	Pour the solution into the mold and loosely place the upper seal. After any large air bubbles have escaped the seal may be replaced. If the mold cools too fast or many bubbles are trapped it may be necessary to heat the mold using a heat lamp. This decreases the solution viscosity and allows the bubbles to escape.
7	Set the mold aside and allow the casting to gel over a 24 hour period. After this time the casting may be removed and placed in a warm water bath to extract the DMSO. Once the solvent is completely removed fabrication is complete.

2.5.5 FT-PVA Hydrogels

Freeze-thaw (FT) PVA polymers are physical gels which are formed by precipitating the polymer from solution. This is typically accomplished by placing the solution in a chilled bath. As this casting begins to cool, adjacent water molecules in the solution congregate and form complexes. Eventually the casting becomes supercooled and ice crystals are nucleated. When the ice formation reaches a certain point the nearby polymer chains are forcibly removed from solution and precipitated. The polymer chains in this precipitate are highly oriented and closely packed so hydrogen bonding is very effective. This allows the polymer to crystallize parallel to the plane of the ice crystals. The casting is then thawed, rehydrated, and frozen again. Subsequent freeze-thaw cycles improve the mechanical strength of the gel by continually crystallizing the remaining amorphous material. The casting may be subjected to many cycles, but the crystalline content will eventually reach a maximum as the amorphous material is consumed. The resulting gels are extremely strong, highly inelastic, and totally opaque. Freeze-thaw PVA polymers do not swell to the extent of conventional PVA gels but the surface is still highly wettable due to the presence of residual amorphous content. These materials also differ from standard PVA gels in that no impurities remain in the casting after gelation. The properties of these gels are highly dependent on the initial solution concentration (porosity), freezing temperature (crystallite size), and the number of freeze-thaw cycles performed (crystalline content).

The FT-PVA hydrogels employed in this study are fabricated by a slightly different method than the traditional freeze-thaw process. This modified process (Table 2.5) begins with a relatively slow cooling in an acetone-dry ice bath. The nucleation and crystallization

stage is allowed to take place in this bath over a four-hour time period. The casting is then removed from the mold and immersed in liquid acetone, dehydrating the remaining amorphous material and solidifying the gel. After washing the sample free of acetone the casting may be rehydrated for later use. Gels fabricated by this method differ from those produced by the standard freeze-thaw process because the crystalline content is reduced. This impacts ultimate strength, but swelling capacity, wettability, and flexibility are improved. More importantly, the gels may be produced more rapidly and at lower cost.

Table 2.4 A process tabulation for modified freeze-thaw poly(vinyl alcohol) hydrogel fabrication. Kodak PVA (99.5% hydrolyzed, 100,000 MW) is used as received. Water is distilled prior to use. Mold design is described in detail in chapter 5.

Step	Directions
1	Clean and assemble the appropriate glass molds as before.
2	Prepare a dry-ice acetone bath.
3	Create a homogeneous 8% PVA solution in distilled water at 85°C.
4	Pour the solution into the mold and loosely place the upper seal. After any large air bubbles have escaped the seal may be replaced. If the mold cools too fast or many bubbles are trapped it may be necessary to heat the mold using a heat lamp.
5	After cooling the solution and ensuring the removal of air bubbles, place the casting in the chilled acetone for four hours.
6	Remove the casting from the mold and quench in acetone for one hour.
7	Wash the casting to remove residual acetone and rehydrate in distilled water.

2.6 Summary

Hydrogel polymers with high water content are generally preferred for medical device applications because they offer enhanced flexibility, wettability, and swelling performance. Ideally, these materials should also exhibit superior mechanical strength. However, in reality a compromise between these attributes must be reached, and designing these materials involves balancing surface properties, which improve with increased water content, and mechanical strength, which tends to degrade. The hydrogels fabricated for this study possess all of the unique surface properties that have been discussed in previous sections, and several methods have been described on the previous pages for the production of hydrogel materials believed to be appropriate for airway device applications. In order to evaluate these materials and identify possible candidates for animal trials a minimum selection criteria of 25 psi tensile strength, 20 psi modulus, 50% water content, and 300% elongation has been defined to eliminate inappropriate materials. These criteria are based primarily on test results which will described later in this document.

CHAPTER 3
SWELLING PERFORMANCE

3.1 Introduction

No examination of hydrogel properties is complete without a description of swelling performance. This is often quantified using equilibrium water content, the mass percentage of water in the gel at the equilibrium swelling point. Many scientists find this value useful because it provides a single generalized quantity that may be used to index mechanical performance, surface properties, and diffusion characteristics. However, it must also be recognized that this approach is oversimplified because it ignores the transitory nature of water in the swollen polymer network. In addition to water content, a complete description of swelling performance must also include kinetic aspects such as the rate of hydration, the rate of dehydration, and associated volume changes. These phenomena may be affected by temperature and humidity, but depend primarily on the chemical nature of the polymer chains and their physical conformation in the network. Chain chemistry is determined by material selection, while physical structure may be defined in terms of entanglements, crosslinking, crystallinity, and porosity. The location of the equilibrium swelling point depends to a large extent on chain chemistry, but because of the influence of physical structure the overall swelling performance is also affected by processing.

The water content of any hydrogel depends primarily on the chemical structure of the polymer. Pendent groups attached to the main chain affect the ability of the gel to attract and retain water molecules, so polymer chains with more hydrophilic substituents will generally exhibit increased swelling capacity. However, water content is also influenced by features which affect free volume, chain mobility, and chain flexibility. An improvement in any of these attributes will generally increase flexibility and water content by facilitating the penetration and retention of water molecules. In many cases the presence of bulky hydrophilic substituents on the main chain (such as the ring group on PVP) contributes significantly to an increase in free volume. The resulting chain separation enhances mobility and provides enlarged internal spaces for the placement of additional water molecules. In other cases the presence of flexible bonds in the main chain (such as the carbon-oxygen bond in polyethylene oxide) increases chain flexibility and reduces the resistance to water passing through the mesh. In either case the end result is an increase in the equilibrium water content. This is ultimately achieved by balancing the forces related to water molecules occupying the internal spaces and the restorative elasticity of the network.

Chemical and physical features that stiffen and immobilize the polymer chains generally reduce flexibility and impede the passage of water molecules through the network. This may occur when bulky groups are incorporated into the main chain, but in practice this is more commonly accomplished through processing. Any increase in crosslink density or crystallinity will stiffen the polymer chains. This reduces chain mobility and the swelling capacity of the gel by excluding water molecules. These same attributes are often adjusted to improve mechanical properties, but swelling performance is frequently impacted as well.

Swelling performance is also significantly affected by porosity. The pore structure develops as the polymer precipitates from the casting solution during polymerization. As previously discussed, this occurs because the polymer has finite solubility in the monomer. The characteristics of this structure frequently may be controlled by adjusting the relative concentrations of water and monomer in the casting solution. This is important because porous hydrogels tend to absorb water more quickly and swell to a greater extent than nonporous gels. The difference in swelling capacity is accounted for by pore water and becomes more pronounced as porosity increases. Still, the presence of pore water has limited effect on flexibility and does not significantly affect volume changes as swelling occurs. It does however, have a very marked effect on solute transport.

3.2 Experiments

3.2.1 Design

The current chapter describes experiments which are designed to adequately describe and quantify the equilibrium water content, hydration kinetics, dehydration kinetics, and volume expansion experienced by several of the hydrogel materials discussed in Chapter 2. The performance of these experiments involves measuring the mass and physical dimensions of several hydrogel samples in various states of hydration. The resulting mass values may then be plotted to form curves illustrating the degree of swelling over time (hydration and dehydration kinetics), or at a single point (EWC). These measurements may also be employed to form curves illustrating volume change over time, or to form correlations between instantaneous water content and the degree of swelling.

3.2.2 Calculations

The instantaneous water content (IWC) is defined as the mass percentage of water in the polymer sample at an unspecified degree of swelling. The equilibrium water content (EWC) is the value of IWC which corresponds to the equilibrium swelling point (complete hydration). Both of these values may be determined gravimetrically using [3.1], where M_w

$$IWC = (M_w - M_d) / M_w \quad [3.1]$$

and M_d are the wet mass and dry mass of the gel sample, respectively. Alternatively, the swelling performance of the gel may be described by [3.2] in terms of instantaneous water

$$IWU = (M_w - M_d) / M_d \quad [3.2]$$

uptake (IWU), which is defined as the mass ratio of water in the sample to the dry weight of the sample. As with water content this calculation may be performed at an unspecified degree of swelling or at the equilibrium swelling point.

3.2.3 Specimens

Two different sample types are used in these studies. The specimens employed in the water content, hydration kinetics, and dehydration kinetics experiments are simple cylindrical discs. The specimens employed in the volume change experiments are cylindrical ring sections. Both specimen types are cast in borosilicate glass test tubes from hydrogel materials fabricated according to established formulae (Chapter 2). The mold which is used to form the volume-change specimens differs from the base mold in the inclusion of a central glass rod. This rod runs the length of the mold and is responsible for forming the central lumen in the ring-shaped specimens. After gelation the castings are de-molded and cut into the form

of flat cylindrical sections, 5 mm in thickness and 15 mm in diameter. The circular section at the center of the ring-shaped specimens is pre-formed to a 5 mm diameter. Before testing impurities are extracted from the specimens by repeated washing in warm distilled water, followed by soaking at 35°C in clean distilled water for a period of at least three days. After extraction the samples are stored in fresh distilled water at 27°C for later use.

3.3 Equilibrium Water Content

3.3.1 Procedure

The wet mass (M_w) is measured after retrieving a fully hydrated specimen from the bath with tweezers and tapping off the excess surface water. The specimen is then desiccated in a convection oven at 85°C for a period of at least 24 hours and re-weighed to yield M_d. The measured values may be substituted into [3.1] to yield the equilibrium water content or [3.2] to yield the equilibrium water uptake.

3.3.2 Results

The composition and water content values for the HEMA-based hydrogels appear in Table 3.1. Referring to this table, it may be seen that the measured value of equilibrium water content for the poly(HEMA) gel is 36%, which is very close to the commonly reported value of 38%. Because the casting water content (30%) is held below the equilibrium value, these gels are single-phase, nonporous, and transparent. Gels that incorporate additional monomers are similar in appearance, but vary in water content according to the type and amount of monomer added. In fact, the addition of either MMA (HM85F) or NVP (HN4030G) results

in the formation of hydrogels quite close in appearance to base poly(HEMA). Both of these gels tend to be single-phase, nonporous, and transparent, but the water content is reduced with the addition of MMA and increased with NVP. In general, neither of these gels will phase separate unless the casting water content is increased or additional hydrophobic monomers are added. Two such materials, the HNM4020G and HNL4020G gels, contain substantial amounts of hydrophobic constituents but do not separate during polymerization because the casting water content is kept fairly low. This may happen during hydration however, particularly if the gamma dose is insufficient to completely polymerize or crosslink the specimen. When this occurs the polymer normally assumes a milky appearance and will feel somewhat softer than the comparable transparent gel.

Table 3.1 Mass percent composition and equilibrium water content (n=3) for poly(2-hydroxyethyl methacrylate) based hydrogels. Other monomers include methyl methacrylate (MMA), lauryl methacrylate (LMA), and vinyl pyrrolidone (NVP).

Designation	Initiator	Casting Composition					EWC
		HEMA	MMA	NVP	LMA	H_2O	
HR	Redox	65%	-	-	-	30%	36%
HM85F	AIBN	85%	15%	-	-	-	20%
HN4030G	Gamma	40%	-	30%	-	30%	73%
HNM4020G	Gamma	40%	10%	20%	-	30%	59%
HNL4020G	Gamma	40%	-	20%	10%	30%	62%

The composition and water content values for the IPN hydrogels appear in Table 3.2. Referring to this table, it may be seen that all of the equilibrium water content values are near 75%. The swelling capacity of these gels appears to depend more on the casting water content than the component ratios. The HEMA monomer and PVP polymer do not mix on a molecular level or covalently bond, and actually tend to form separate domains during polymerization. In fact, these materials will often phase separate during hydration because the two domains have differing swelling capacities. The size and distribution of these domains depends on the HEMA : PVP ratio and the casting water content. Increasing casting

Table 3.2 Mass percent composition and equilibrium water content (n=3) for HEMA-PVP based interpenetrating polymer network (IPN) materials.

Designation	Casting Composition			EWC
	HEMA	PVP	H_2O	
IPN15	18.0%	12.0%	70.0%	80%
IPN20	20.0%	10.0%	70.0%	78%
IPN25	21.5%	8.5%	70.0%	77%
IPN30	22.5%	7.5%	70.0%	77%
IPN35	23.3%	6.7%	70.0%	77%
IPN40	24.0%	6.0%	70.0%	76%
IPN45	24.5%	5.5%	70.0%	76%

water at a given material composition disproportionately swells the PVP domains, promoting phase separation. This increases the average pore size and enhances the wettability of the surface, but also weakens the material. The domain size may be reduced and phase separation avoided by lowering the casting water content, but this is not normally permanent unless crosslinking is sufficient to effectively restrict chain migration. As the gel composition becomes less rich in PVP the tendency to phase separate is reduced and mechanical strength improves, but the IPN becomes less porous and wettability suffers.

The composition and water content values for the PVA hydrogels appear in Table 3.3. Referring to this table, it may be seen that there is a wide variation between the water content values for the sample types, particularly the standard (PVA-S) and freeze-thaw (PVA-F) hydrogels. This is expected of course, because while the two gels are chemically similar, the resulting microstructures are radically different. Standard PVA gels are almost completely amorphous, nonporous, and transparent. The water contents of these gels tend to be rather high and they are capable of suffering extensive plastic deformation without failure. The mechanical properties of these gels depend on the composition of the solvent, the polymer concentration, and heat history. Freeze-thaw PVA gels, on the other hand are semi-crystalline, microporous, and totally opaque. The crystalline regions form insoluble hydrophobic domains as they precipitate from the polymer mass. These crystalline regions strengthen the gel, restrict plastic deformation, and account for the reduced water content of the material. The amorphous regions are porous and swell extensively, but the overall properties of the gel are still governed by the crystalline microstructure. Overall properties are adjusted by altering freezing temperature and soaking time rather than component ratios.

Table 3.3 Mass percent composition and equilibrium water content (n=3) for PVA-based hydrogels. All samples were cast from an 8% PVA solution in either distilled water or a mixed (50%) solvent consisting of dimethyl sulfoxide (DMSO) in water. Treatment refers to the length of heat treatment applied to conventional PVA gels or the number of temperature cycles applied to the free-thaw PVA gels.

Designation	Solvent	Treatment	EWC
PVA-S-1	Mixed	4 hour air-dry	84%
PVA-S-2	Mixed	24 hour air-dry	78%
PVA-S-3	Mixed	24 hour oven-dry	45%
PVA-F-1	Water	One cycle	52%
PVA-F-2	Water	Two cycles	46%
PVA-F-3	Water	Three cycles	47%

3.4 Hydration Kinetics

3.4.1 Procedure

This experiment begins with the gel sample in an intermediate hydration state (typically 50% of the equilibrium value), and is performed with the sample in distilled water at 27°C. After a measured time interval the sample is removed from the bath with tweezers, the excess water is tapped off, and the mass (M_w) is measured. The sample is then replaced in the bath to await the next measurement. This sequence of events is generally repeated until the sample approaches complete hydration, but may be terminated at any time. After termination the specimen is desiccated in a convection oven at 85°C for a period of at least 24 hours and re-weighed (M_d). The resulting values may be used to construct hydration curves based on water content or water uptake as previously described.

3.4.2 Results

Most hydrogel materials follow a basic three-mode hydration curve (Figure 3.1) which varies in shape according to the chemical nature and pore structure of the gel. In the lower portion (region 1) of the curve the gel is nearly dehydrated and swelling kinetics are poor (slow water uptake). In this state the polymer chains are in close proximity and inter-chain polar interactions predominate, resulting in very strong hydrogen bonding. Basically, in this region the network is tightly packed and the chains have a greater attraction for each other than the water molecules. At the opposite end (region 3) of the curve the polymer network density is reduced by the presence of abundant water molecules. In this state the hydrophilic pendent groups are effectively shielded from one another and nearly prevented from attracting additional water molecules. Also, in this region the gel is nearly swelled to capacity and the elastic response of the network prevents the entry of additional molecules. In between these two extremes is the desired operating region where swelling is relatively rapid. In this area of the curve the chains are incompletely hydrated so the pendent groups still attract

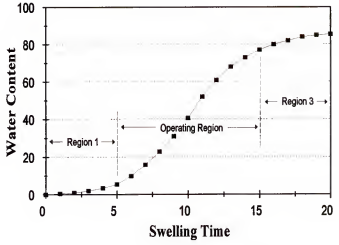

Figure 3.1 Ideal swelling curve. Slope increases in the center of the curve where water uptake is the greatest. This is the desired operating region.

water molecules. Also, because the network is not highly stressed water molecules are not prevented from entering the mesh. The most significant changes in volume and wettability occur in this region of the curve.

The experimental results for individual materials are illustrated in Figures 3.2 through 3.6. In addition, a plot comparing these results appears in Figure 3.7. To reduce the plot size and highlight the operating region, these curves are restricted to region 2 through complete hydration. The hydration experiment results for the poly(HEMA) hydrogel and the HN4030G copolymer are plotted in Figures 3.2 and 3.3, respectively. Referring to these figures it may be seen that the response curves are very similar for both materials. These two plots feature

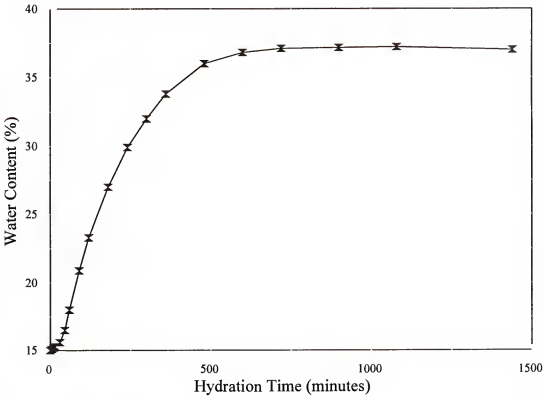

Figure 3.2 Hydration response curve (n=3) for the poly(HEMA) hydrogel. The linear swelling rate(initial slope) is estimated over roughly the first three hour portion of the plot.

the characteristic (nearly) linear hydration region followed by a flattening termination plateau. The primary difference between these two materials is in the EWC, which is much greater for the copolymer. The high water content enhances the swelling capacity and porosity of this material, and probably accounts for the increased swelling rate (3.75 versus 3.40) of the HN4030G copolymer over the standard poly(HEMA) hydrogel.

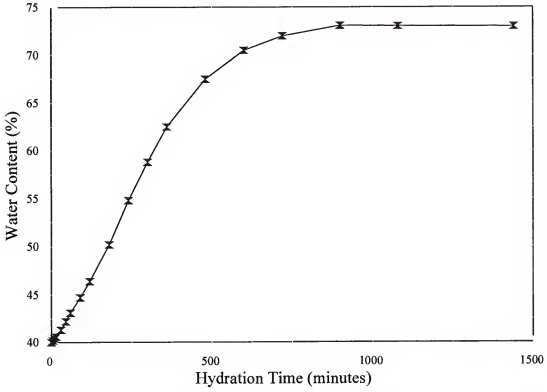

Figure 3.3 Hydration response curve (n=3) for the HN4030G copolymer gel. The swelling rate for this material is estimated over roughly the first six hour portion of the plot.

The hydration experiment results for the IPN30 hydrogel are plotted in Figure 3.4. Referring to this figure it may be seen that the initial slope of the curve is rather steep (linear swelling rate), with a smooth transition from the operating region to the termination plateau.

It is interesting to compare these results with the HN4030G copolymer plot, because the two materials have a similar composition but different microstructure. The copolymer has a HEMA:PVP ratio close to 1.3, while the IPN ratio is 3.0. In spite of this fact both materials exhibit an equilibrium water content near 75%. On this basis alone it might be expected that the two materials would have similar swelling rates but this is not the case. In fact, the IPN has a linear swelling rate (7.00) that is nearly twice the value of the HN4030G copolymer. This occurs even though the IPN30 hydrogel has roughly half the PVP content of the copolymer. The IPN pore structure created by domain separation during polymerization probably increases the swelling rate by facilitating the penetration of water molecules.

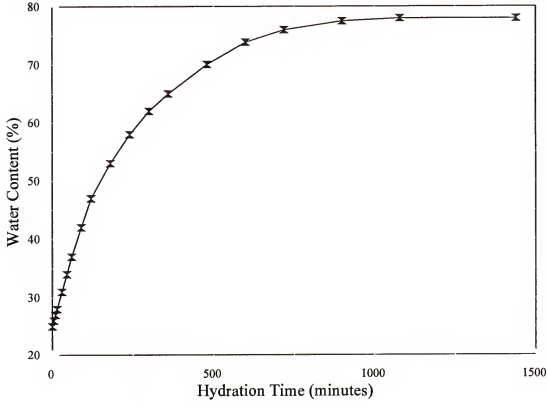

Figure 3.4 Hydration response curve (n=3) for the IPN30 hydrogel. The linear swelling rate is estimated over roughly the first three hour portion of the plot.

The hydration experiment results for the PVA-S-1 and PVA-F-1 hydrogels are illustrated in Figures 3.5 and 3.6, respectively. These two materials also make an interesting comparison because they are chemically identical but structurally dissimilar. In fact, the standard PVA gels are almost totally amorphous, while the freeze-thaw gels are semi-crystalline. This helps to explain the difference in water content (86% versus 47%) and swelling rate (13.0 versus 5.4), both of which are greater for the amorphous gel. The rather abrupt shift between the hydration region and termination plateau for the PVA-F-1 gel may be due to porosity. This is not caused by phase separation, but the precipitation of crystallites during gelation. Figure 3.7 illustrates all results on a single graph.

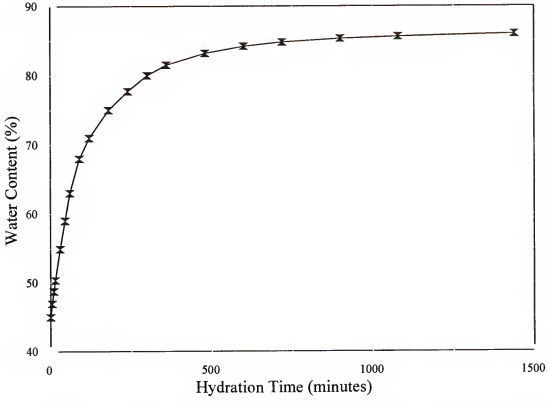

Figure 3.5 Hydration response curve (n=3) for the amorphous PVA-S-1 hydrogel. The linear swelling rate is estimated over the first two hour period of the plot.

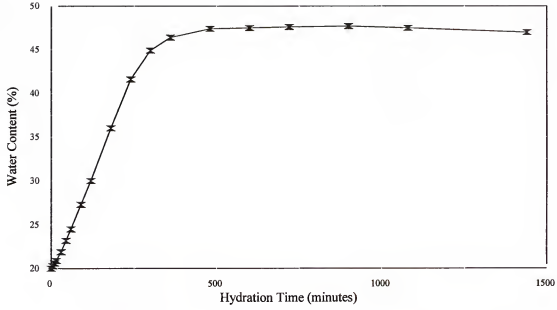

Figure 3.6 Hydration response curve (n=3) for the semi-crystalline PVA-F-1 hydrogel. The linear swelling rate is estimated over roughly the first four-hour portion of the plot.

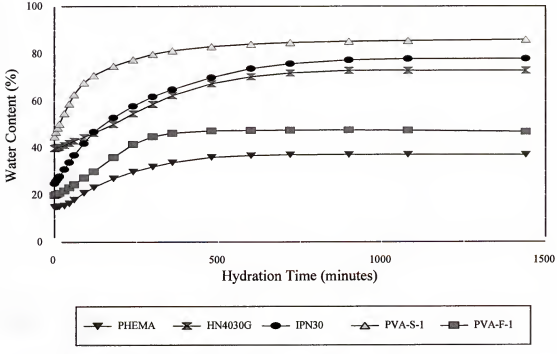

Figure 3.7 Hydration response curves for all tested hydrogels.

3.5 Dehydration Kinetics

3.5.1 Procedure

This experiment begins with a fully hydrated gel sample. This is removed from wet storage using tweezers, the excess water is tapped off, and an initial mass measurement (M_w) is taken. The specimen is then placed flat on a dry glass plate at 27°C and 55% relative humidity. After a measured time interval the sample is removed from the plate with tweezers and the sample mass is measured again. The sample is then replaced on the plate for the next measurement. It is important to ensure that the specimen is placed with the same side facing upward or discontinuities in the curve will result. This sequence of events may be repeated indefinitely or until the sample approaches complete dehydration. Once the measurements are completed the specimen may be desiccated in a convection oven at 85°C for a period of at least 24 hours, then re-weighed to yield (M_d). The resulting values may be plugged into [3.1] to create a dehydration curve based on water content.

3.5.2 Results

The dehydration experiment results are illustrated in Figure 3.8 (HEMA-based gels), Figure 3.9 (IPN gels), Figure 3.10 (standard PVA), and Figure 3.11 (FT-PVA). Each of these plots have the same basic shape and describe a nearly linear mass loss after the initial portion of the curve. Deviations in linearity generally occur near the beginning of the dehydration cycle and typically become more pronounced as the water content of the material increases. Referring to these figures, it is clear that the nonlinear regions are more pronounced in the most hydrophilic materials. Porosity generally increases with water content, so initial

dehydration is probably more rapid in these materials due to increased pore water evaporation. This initial rate slows as the material dehydrates and the pores at the surface begin to constrict. Eventually an equilibrium is reached between water passing through the core and evaporation from the surface. This is reflected in the latter portion of the curves. The freeze-thaw PVA hydrogels deviate from this behavior and exhibit a greater initial mass loss rate than most other materials. The dehydration curve for these gels is also nonlinear for a much longer segment of the cycle. This is probably due to the complex combination of crystalline and amorphous material in the FT-PVA microstructure.

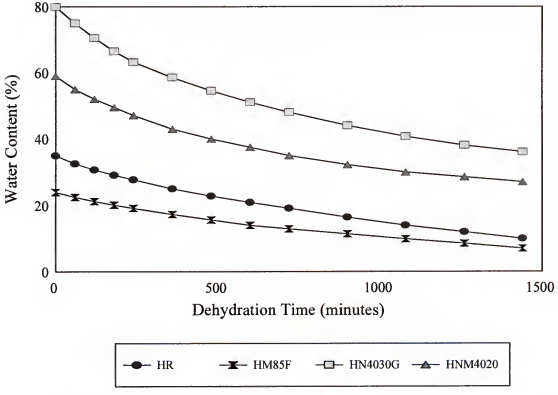

Figure 3.8 Dehydration experiment results (n=3 each material) for HEMA-based hydrogel materials. Note that the curves tend to become more linear as the equilibrium water content and porosity of the materials increase.

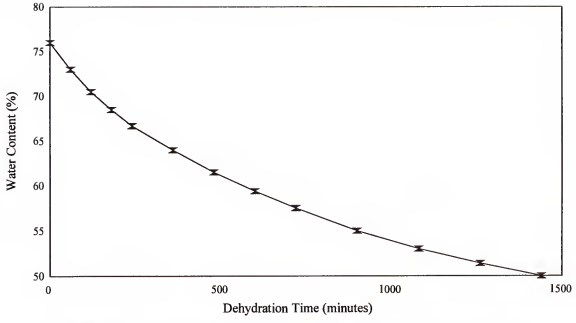

Figure 3.9 Dehydration experiment results (n=3) for IPN30 hydrogel. Note that the curve is approximately linear from the middle to the end of the cycle, with the nonlinear portion occurring at the beginning. This behavior is probably related to initial pore water loss.

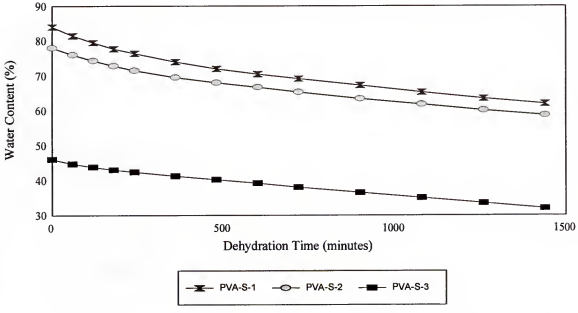

Figure 3.10 Dehydration experiment results (n=3 each material) for standard PVA hydrogels. Note that the curves are nearly linear with the exception of PVA-S-1 and PVA-S-2.

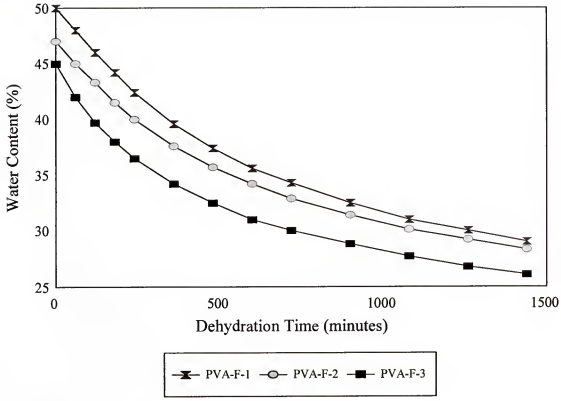

Figure 3.11 Dehydration experiment results (n=3 each material) for freeze-thaw PVA hydrogels. These plots are nonlinear up to the latter stages of dehydration.

3.6 Volume Change

3.6.1 Procedure

This experiment involves measuring both the mass and linear dimensions of a specimen as it dehydrates over time. The required samples are cast in a ring-shaped (Figure 3.12) configuration from the standard PVA-S-1 hydrogel. To begin the experiment the specimen is removed from the bath with tweezers, the excess water is tapped off, and an initial mass measurement (M_w) is taken. The length, internal diameter, and external diameter of the specimen are then measured and recorded. The specimen is then placed flat on a clean

glass plate at 27°C and 55% relative humidity to dry. At measured intervals the sample is re-weighed, re-dimensioned, and replaced on the glass plate. When conducting this experiment it is important to remember to place the sample in the same position after each cycle, because improperly placing or 'flipping' the sample may introduce discontinuities into the data. In general, this sequence of events may be repeated until complete dehydration occurs, but for this study the drying stage was terminated after 24 hours. At this time the specimen is removed and desiccated in a convection oven at 85°C for a period of at least 24 hours, then re-weighed to yield M_d. The resulting mass and dimension values may be used in conjunction with [3.1] to plot a volume-time plot, or to form a correlation between volume and water content.

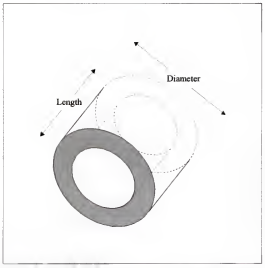

Figure 3.12 Specimen for volume change experiments. Both diameters are measured but no correlation is developed for I.D.

3.6.2 Results

The objective of this experiment is the development of a simple expression relating water content to sample dimensions. This will allow an estimate of part volume based on a knowledge of the composition and water content of the material. It should also assist in developing and predicting the performance of prototype airway devices. The data used to derive these relations is based on 'normalized' dehydration curves. Basically, normalization is a simplifying step that involves adjusting the axes so that the greatest measured value is

equal to 100%. For example, the diameter measurements may be divided by the initial diameter so that at t_o the normalized diameter is equal to 100 percent.

The results for the experiment are illustrated in Figure 3.13 (length), Figure 3.14 (outer diameter), and Figure 3.15 (volume). In addition, a straight-line is fitted graphically to the upper portion of each curve. The equations shown on the figures correspond to these lines. However, because of the way the lines are fitted these relations are completely inaccurate below 50% hydration, and it is important to recognize that these expressions estimate water content at or above the desired operating region. Hydration and dehydration curves are dissimilar, and the samples in these studies are not in equilibrium. Still, these expressions should provide some information limited to this portion of the curve.

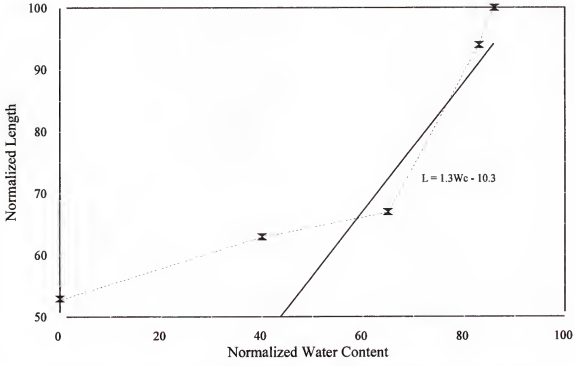

Figure 3.13 Derived relation between water content and sample length (n=3). The abscissa is normalized to the equilibrium water content value.

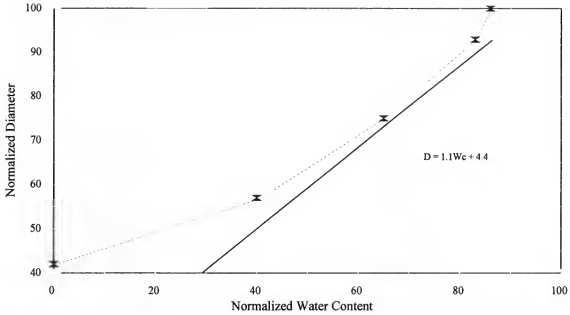

Figure 3.14 Derived relation between water content and sample external diameter (n=3). The abscissa is normalized to the equilibrium water content.

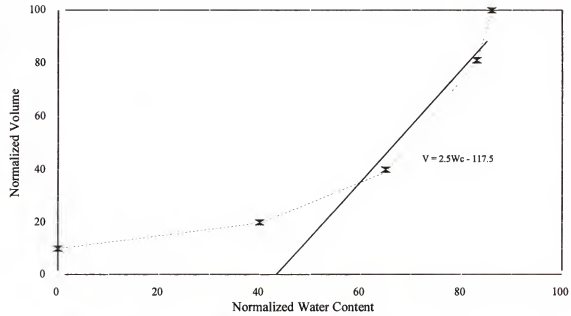

Figure 3.15 Derived relation between water content and sample volume (n=3). The abscissa is normalized to the equilibrium water content.

3.7 Summary

The water content of any hydrogel depends primarily on the chemical structure of the polymer. Pendent groups attached to the main chain affect the ability of the gel to attract and retain water molecules, so polymer chains with more hydrophilic substituents will generally exhibit increased swelling capacity. However, water content is also influenced by features which affect free volume, chain mobility, and chain flexibility. An improvement in any of these attributes will generally increase swelling capacity by facilitating the penetration and retention of water molecules. In contrast, chemical and physical features that stiffen or immobilize the polymer chains will generally impede the passage of water through the network. This may occur when bulky groups are incorporated into the main chain, but in practice is more commonly accomplished through processing. Increasing the crosslink density or crystalline content will stiffen the polymer chains, reducing chain mobility and swelling capacity by excluding water molecules. These same attributes are often adjusted to improve mechanical properties, but swelling capacity is frequently impacted as well. In order to describe and quantify the performance variations that occur relative to changes in gel composition a series of material selection criteria were described in the previous chapter. In the current chapter several candidate materials were examined for water content, hydration kinetics, dehydration kinetics, and volume change. Based on the results of these studies several gel materials conforming to the criteria were identified for further testing.

CHAPTER 4
MECHANICAL PERFORMANCE

4.1 Introduction

Hydrogel mechanical performance is directly related to the degree of swelling, and in general these materials tend to become stronger and less compliant as the water content is reduced. Ideal hydrogels possess both highly wettable surfaces and excellent mechanical properties, but in reality this ideal is difficult to achieve. Because ideal surface and bulk properties appear to be mutually exclusive, it is often necessary when designing a hydrogel for a particular application to choose between favoring mechanical performance and surface characteristics. In applications requiring significant strength a material with low water content may perform adequately. However, because most of the beneficial surface properties attributed to these materials are associated with wettability and high water content the surface characteristics of this material will fall far short of the ideal. The effective design of hydrogel materials therefore requires an understanding of the application so that a proper balance between acceptable surface properties and adequate mechanical performance may be achieved. The relative importance of bulk and surface properties in designing this material is unique to each application, and much of the published work on this subject deals with the resolution of these seemingly incompatible goals.

Hydrogel surface properties typically improve as the equilibrium water content is increased. This may be accomplished by augmenting the syrup with more hydrophilic monomers or by modifying processing parameters to increase porosity. This strategy attracts additional water molecules which penetrate the polymer mesh and further separate the chains. The resulting increase in free volume enables easier chain flexing and uncoiling, so the flexibility of the gel is enhanced. However, entanglements are reduced and chain mobility is improved so the material has a greater tendency to deform under stress. In addition, because the network density is reduced there are fewer polymer chains per unit area to support applied loads. This results in a net reduction in tensile strength.

Hydrogel tensile strength generally improves as the water content is decreased. However, reducing the water content is not usually an option because of the negative impact on surface properties. When possible it is generally more desirable to improve strength without impacting wettability. While this may not always prove feasible, it is important to minimize the effect of changes designed to improve strength on other properties. Common methods for enhancing strength include crosslinking and the addition of more hydrophobic monomers. Chemical and physical crosslinks act to constrain the network, bringing the chains closer together to increase cohesive forces. The inclusion of hydrophobic monomers stiffens the resulting copolymer through the addition of bulky side groups. In both cases chain mobility is reduced and strength is improved. Unfortunately, water content is also reduced so effective free volume decreases and flexibility is negatively impacted. In practice, hydrogel materials with a water content greater than seventy percent are expected to be both highly flexible and exhibit the best surface properties, but these materials also tend to be very

weak. When the water content is below forty percent these same materials tend to become much stronger but are also more rigid with less favorable surface properties. The target equilibrium water content depends on the specific application and host environment, but in general an attempt is made to maximize this value while maintaining acceptable mechanical performance. As a rule of thumb, a balance of surface properties, flexibility, and strength may be achieved by holding the water content between forty and seventy percent.

4.2 Experiments

There are no standards designed specifically for the mechanical testing of hydrogels or swelled polymers. Published tensile studies on these materials have been based on ASTM D412, ASTM D638, ASTM D882, other ASTM standards, some foreign standard, or no standard at all. Dynamic mechanical data on these materials is collected infrequently, but the scientists that have performed these experiments typically do not follow established standards. This is unfortunate because the results of these experiments are highly dependent on both technique and sample preparation. In particular when the values involved are very small, a slight change in technique may produce a significant variation in measured results. Because there are no reliable standards to follow it is nearly impossible to compare results between authors. There is no plausible reason for this situation to continue, because while hydrogels are a relatively new class of materials, the initial work by Wichterle was published almost forty years ago. The development of standards would allow reliable comparisons between published studies and would therefore represent a significant advance for this important class of materials. Perhaps this oversight will be corrected in the near future.

This chapter is devoted to the description of a series of tensile and creep experiments performed on the previously discussed candidate hydrogel materials. The tensile tests are loosely based on ASTM D638-91A, while the creep experiments are both nonstandard and unique. Because these test procedures do not follow accepted standards the results are useful primarily for comparison with other materials tested in this document. The results of these experiments are detailed on the following pages.

4.3 Tensile Tests

4.3.1 Specimens

The tensile specimen fabrication process begins with 2 mm thick hydrogel sheet. This is cast in a mold that is constructed from two 12 inch square glass plates sealed with silicone tubing. These plates are also separated by 2.1 mm plastic spacers to maintain uniform gel thickness. The mold is lined with Teflon coated polyester film to facilitate removal and to prevent the casting from sticking to the mold. Once polymerization is complete the casting is removed from the mold and several specimens (Figure 4.1) are cut from the center portion of the sheet using a standard die and press. This die is designed to produce the 'Type

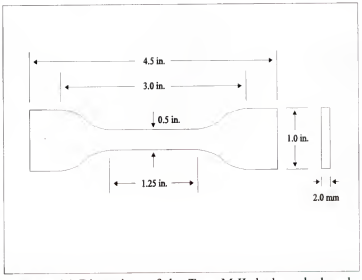

Figure 4.1 Dimensions of the Type M-II dogbone hydrogel specimens specified by ASTM D638 in tensile tests.

M-II' dogbones specified by the standard for nonrigid plastics less than 4 mm in thickness. These specimens are washed in distilled water at 35°C for at least 8 hours, then placed in clean distilled water at 27°C for at least three days prior to testing.

4.3.2 Procedure

All tensile tests are performed on an Instron model 1122 tensile testing machine. The equipment is powered on and allowed to warm up for at least thirty minutes prior to each testing session. The crosshead position is then adjusted to provide a 2.5 inch grip separation and the machine is calibrated using weight standards. In order to provide accurate results the equipment must be calibrated at the start of each testing session and recalibrated whenever the load cell is changed. Before each experiment the specimen to be tested is removed from the water bath and exact gage dimensions are measured using digital calipers. After this data is recorded paper tabs are placed over the grip sections at each end. These tabs serve to prevent the gel material from extruding or slipping out of the grips. The specimen is then placed into the grips so that the sample axis and machine axis are aligned and the grip pressure is set 30 psi. The experiment is initiated by moving the crosshead downward at a constant (1 inch per minute) stroke rate. During the experiment distilled water is sprayed on the gage section every 5 seconds using an atomizer. This step is very important because the mechanical properties of the specimen will be seriously affected if the gel does not remain hydrated. While the crosshead is moving the stress in the sample is measured with a load cell and collected with digital data acquisition equipment. After the specimen fails the crosshead is replaced in the start position, another specimen is loaded into the grips, and the sequence

of events is repeated. A total of thirty specimens are generally tested for each sample type, with a maximum of five discarded due to testing anomalies (failure or slippage). The collected data allows an engineering stress-strain curve to be plotted for each sample, and the failure strength, estimated modulus, and percent elongation values are derived from these plots. This data is averaged and reported as mean values for each sample type.

4.3.3 Results

The tensile test results for the HEMA-based hydrogels appear in Table 4.1. Referring to this table it is interesting to compare the values for the pure poly(HEMA) gel to the more complex copolymers and terpolymers. As expected, the data show that these materials become stronger, stiffer, and tougher as hydrophobic monomers are added to the syrup. The

Table 4.1 Tensile test data (n=25) for HEMA-based hydrogels. Raw data was unavailable so descriptive statistics were derived assuming a 22 % coefficient of variation V. Author finds that V is typically 20 ± 5 % for these materials. Data presented as $\mu \pm \sigma$.

Designation	Strength (psi)	Modulus (psi)	Elongation (%)
HR	95 ± 21	125 ± 28	140 ± 31
HM85F	245 ± 54	390 ± 86	75 ± 17
HN4030G	35 ± 8	55 ± 12	290 ± 64
HNM4020G	110 ± 24	210 ± 46	145 ± 32
HNL4020G	145 ± 32	260 ± 57	180 ± 40

data also show that these gels become weaker, softer, and much more flexible with the addition of hydrophilic monomers. As previously stated, this change in mechanical behavior may be attributed to the influence of water content on chain mobility and free volume. For example, the poly(HEMA) hydrogel (36% EWC) has a strength of 95 psi, a modulus of 125 psi, and an elongation at failure of 140%. When this material is copolymerized with MMA (HM85F) the water content is halved while the strength is almost tripled. This severe reduction in water content (20% EWC) causes the gel to become very stiff and inelastic, as the modulus and elongation values change to 390 psi and 75%, respectively. In contrast, copolymerizing poly(HEMA) with NVP (HN4030G) causes a very large reduction in both strength and modulus while the elongation is doubled.

The addition of MMA and LMA to a HEMA-NVP copolymer also has predictable results. Referring once more to Table 4.1 it may be seen that the tensile strength and modulus values for the HNM4020G and HNL4020G terpolymers are much greater than the values for the HN4030G copolymer. The ultimate elongation values for these terpolymers are also much lower than the value for the copolymer. These differences are attributed to the significant decrease in water content and chain mobility caused by the addition of the hydrophobic monomers. In spite of the reduction in water content and flexibility, these terpolymers may have some potential in medical applications due to their excellent mechanical properties. However, the HN4030G copolymer should still prove superior in non load bearing applications that require a highly wettable surface. In fact, the high water content (73%) of this material imparts an almost unparalleled lubricious surface. Figures 4.2 - 4.4 illustrate the mechanical properties of these materials in relation to water content.

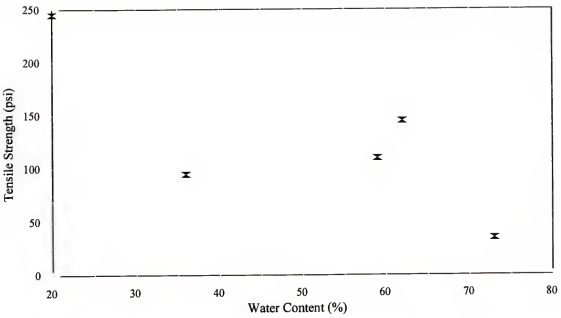

Figure 4.2 Tensile strength versus equilibrium water content (n=25) for all HEMA-based hydrogel materials. See descriptive statistics note on Table 4.1.

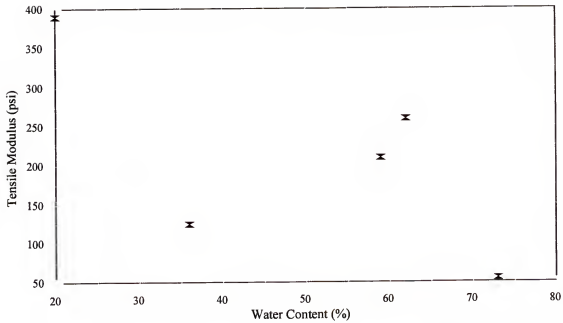

Figure 4.3 Tensile modulus versus equilibrium water content (n=25) for all HEMA-based hydrogel materials. See descriptive statistics note on Table 4.1.

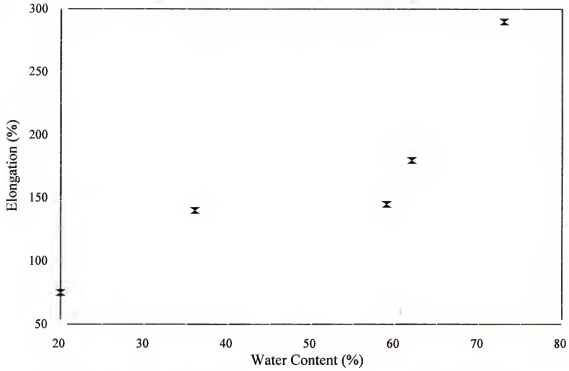

Figure 4.4 Elongation at failure versus equilibrium water content (n=25) for all HEMA-based hydrogel materials. See descriptive statistics note on Table 4.1.

The tensile test results for the IPN hydrogels appear in Table 4.2. Moving down this table (from IPN20 through IPN40) the HEMA:PVP ratio increases and there is a noticeable change in the look and feel of the material. Referring to this table it may be seen that the samples become stronger, stiffer, and less compliant as the component ratio is increased. At the lower end of the spectrum (IPN20) the material is extremely soft and lubricious with an opaque white appearance. As the amount of HEMA monomer in the syrup increases the hydrogel becomes stronger and stiffer, but flexibility is reduced. At the same time the surface becomes less lubricious and the material begins to turn translucent. When the IPN50 composition is reached the gel becomes nearly transparent and similar to poly(HEMA) in

Table 4.2 Tensile test data (n=25) for IPN hydrogels. Raw data was unavailable so descriptive statistics were derived assuming a 22 % coefficient of variation V. Author finds that V is typically 20 ± 5 % for these materials. Data presented as $\mu \pm \sigma$.

Designation	Strength (psi)	Modulus (psi)	Elongation (%)
IPN20	15 ± 3	19 ± 4	590 ± 130
IPN25	21 ± 5	28 ± 6	480 ± 106
IPN30	28 ± 6	36 ± 8	445 ± 78
IPN35	36 ± 8	55 ± 12	360 ± 79
IPN40	48 ± 11	72 ± 16	240 ± 53

both appearance and mechanical performance. These results are particularly interesting because there is essentially no variation in water content as this ratio is changed. In fact, the water content values are nearly identical (about 75%) for each of the listed samples. Since there is no change in water content as the component ratio increases, there must be some compensating variation in pore volume. At any rate, pore water does not intimately contact the polymer chains and therefore does not have the same effect as hydrating water on flexibility. Still, some type of phase separation must be occurring because light transmission through the gel is reduced as the PVP content increases. One explanation for this phenomenon is the formation of PVP domains. As the HEMA:PVP ratio decreases the number and size of these domains would probably increase. Since these domains are formed from a polymer that is much more hydrophilic than poly(HEMA), the domain water content would be greater than in the bulk, further enhancing flexibility and reducing strength. The

bulk water content would remain unchanged in this scenario because the amount of 'free space' to accommodate swelling water would be locked in during casting. This is not shown in Table 4.2, but is evident in other experiments which show the dependence of equilibrium water content on the casting water content. Figures 4.5 - 4.7 illustrate the mechanical properties of these materials in relation to water content.

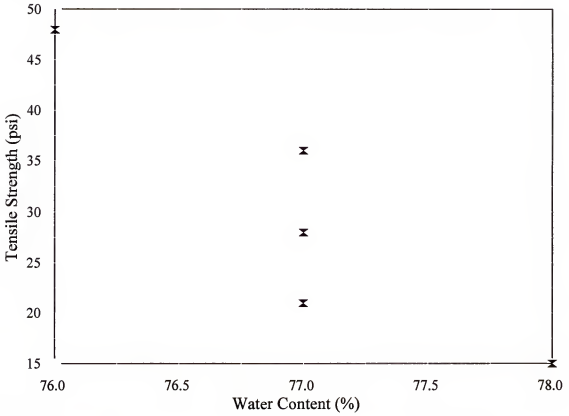

Figure 4.5 Tensile strength versus equilibrium water content (n=25) for all IPN hydrogel materials. See descriptive statistics note on Table 4.2.

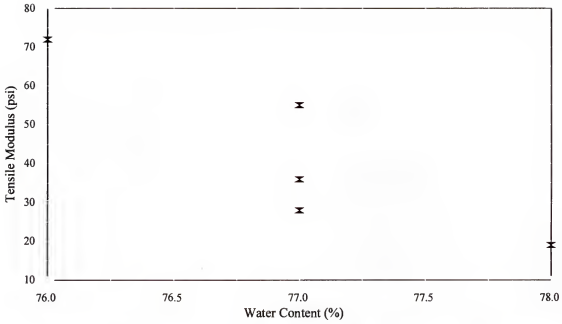

Figure 4.6 Tensile modulus versus equilibrium water content (n=25) for all IPN hydrogel materials. See descriptive statistics note on Table 4.2.

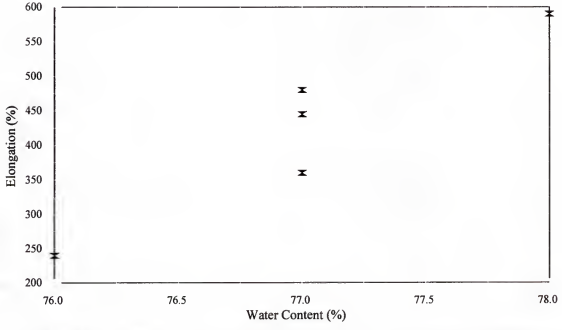

Figure 4.7 Elongation at failure versus equilibrium water content (n=25) for all IPN hydrogel materials. See descriptive statistics note on Table 4.2.

The tensile test results for both the standard and freeze-thaw PVA hydrogels appear in Table 4.3. Referring to the data for the standard PVA gels it may be seen that there are two distinct levels of performance. Each of these materials (the first three) are identical in composition and differ only in drying procedure. The PVA-S-1 gel is air dried for 4 hours, while the PVA-S-2 gel is air dried for 24 hours. The water content values for these two materials are nearly the same (approximately 80%) and the mechanical performance is also very similar. This is probably due to the fact that even after 24 hours the hydrating water is not completely removed. The presence of this water not only plasticizes the material, but also separates the chains and prevents efficient hydrogen bonding. This causes the two air-dried gels to have similar appearance and mechanical performance after rehydration. In contrast, when a similar gel is oven dried (PVA-S-3) both the pore and hydrating water is removed. This allows the polymer chains to more closely approach, improving the packing efficiency. This in turn promotes hydrogen bonding and reduces the ultimate degree of swelling once the gel rehydrates. Improved hydrogen bonding is partially responsible for the relative increase in strength and modulus values exhibited by the PVA-S-3 gel.

Commercially available PVA is generally atactic. However, because the hydroxyl group is very small, crystallinity is still possible, especially when the chains are closely packed. Crystallinity probably plays a negligible role in the strength increase of standard PVA gels because there is no noticeable change in transparency during oven drying. In contrast, freeze-thaw PVA gels are obviously highly crystalline. In fact, even after a single freeze-thaw cycle (PVA-F-1) these gels become totally opaque, the water content is reduced to near 50%, and there is a very large increase in strength and modulus. Subsequent cycles

Table 4.3 Tensile test data for PVA-S (n=25) and PVA-F (n=1) hydrogels. Raw data was unavailable so descriptive statistics were derived assuming a 22 % coefficient of variation V. Author finds that V is typically 20 ± 5 % for these materials. Data presented as $\mu \pm \sigma$.

Designation	Strength (psi)	Modulus (psi)	Elongation (%)
PVA-S-1	25 ± 6	15 ± 3	280 ± 62
PVA-S-2	25 ± 6	24 ± 5	240 ± 53
PVA-S-3	110 ± 24	190 ± 42	305 ± 67
PVA-F-1	1065	1420	75
PVA-F-2	1170	1215	55
PVA-F-3	1135	1510	60

reduce the water content and increase strength even further by crystallizing portions of the remaining amorphous material. However, the change in crystallinity must diminish incrementally after the first cycle because the reduction in water content and increase in strength and stiffness becomes increasingly smaller. This may be attributed to the fact that most of the available material has already been crystallized after the first cycle. At any rate, because the elongation is greatly reduced as the crystalline content increases it may be advantageous (for certain medical applications) to discontinue processing after the first cycle. This strategy would help to save both time and expense. Graphical plots of strength, modulus, and elongation with respect to water content for the standard PVA hydrogels may be seen in Figures 4.8 - 4.10. The mechanical properties of the freeze-thaw PVA hydrogels with respect to water content are summarized in Figures 4.11 - 4.12.

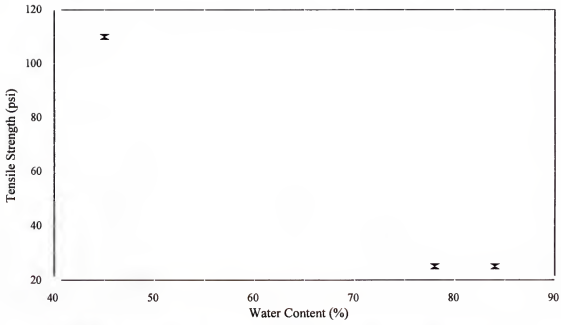

Figure 4.8 Tensile strength versus equilibrium water content (n=25) for all standard PVA hydrogel materials. See descriptive statistics note on Table 4.3.

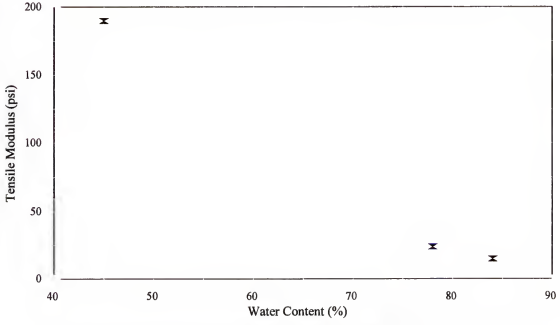

Figure 4.9 Tensile modulus versus equilibrium water content (n=25) for all standard PVA hydrogel materials. See descriptive statistics note on Table 4.3.

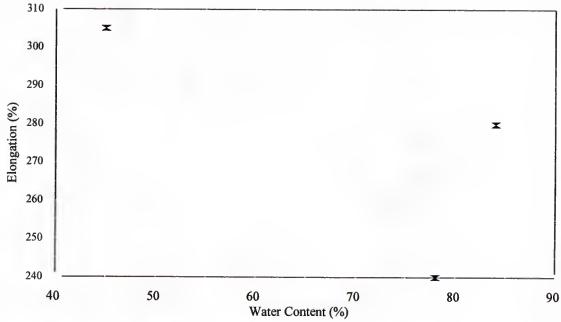

Figure 4.10 Elongation at failure versus equilibrium water content (n=25) for all standard PVA hydrogel materials. See descriptive statistics note on Table 4.3.

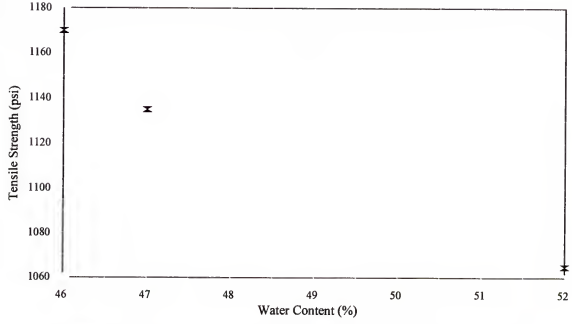

Figure 4.11 Tensile strength versus equilibrium water content (n=1) for all freeze-thaw PVA hydrogel materials.

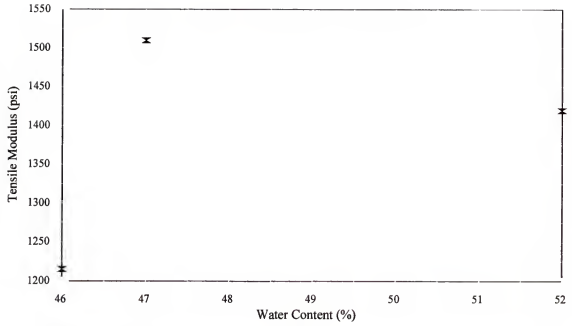

Figure 4.12 Tensile modulus versus equilibrium water content (n=1) for all freeze-thaw PVA hydrogel materials

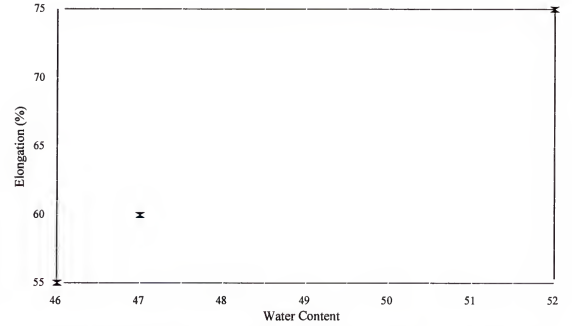

Figure 4.13 Elongation at failure versus equilibrium water content (n=1) for all freeze-thaw PVA hydrogel materials.

4.4 Creep Tests

4.4.1 Specimens

The creep tests employ solid cylindrical rods 5 mm in diameter and 10 cm in length. These are cast from various hydrogel formulations in 12 inch long tubular glass molds. After casting the specimens are removed from their molds, cut to the appropriate length, and washed in distilled water at 35°C for at least 24 hours. This water is changed several times to ensure that all impurities are extracted. After extraction a 1.5 cm section at each end of the specimen is air dried and fiber washers are placed over the ends (Figure 4.14). Cotter pins are then driven through the dry sections to maintain the location of the washers. After placing the pins silicone sealant is applied over the dried gel sections and allowed to cure in air at room temperature for at least 24 hours. After curing, the end cap sections are secured with shrink tubing to ensure that the dried sections do not swell. The finished specimens are then inspected for defects and placed in a room temperature water bath for later use.

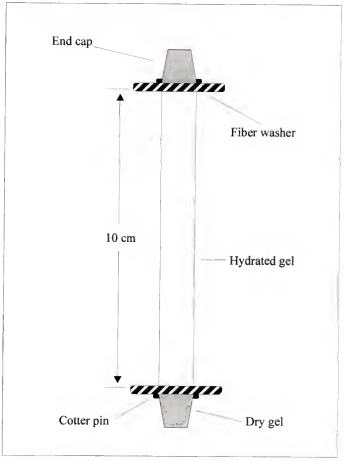

Figure 4.14 Creep specimen. These are cast from several of the candidate hydrogel materials previously discussed.

4.4.2 Procedure

The creep experiments employed in this study are performed on custom-designed equipment. This apparatus (Figure 4.15) is constructed from 4 mm aluminum plate and allows the suspension of a separate mass beneath each specimen. The top plate accommodates a maximum of four samples and is held firmly in place with bolts and pins. The creep test is initiated by securing one or more specimens in the top plate and submerging the assembly in a water tank. Immersing the samples is necessary in order to prevent swelling-related changes in mechanical properties that might otherwise alter the results. The mass (spring steel) loaded onto the hanger is different for each sample type and is selected to provide an approximate 50% initial elongation. No correction is applied for buoyancy. After the load is applied and the apparatus is submerged the initial deflection may be

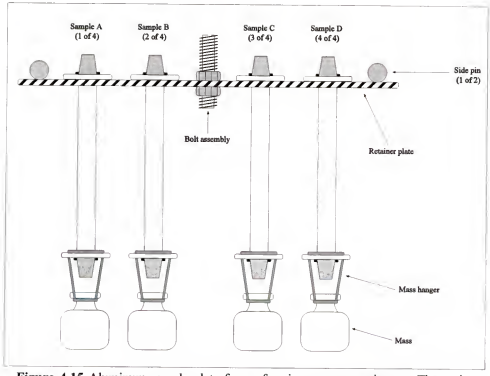

Figure 4.15 Aluminum sample plate for performing creep experiments. The entire apparatus is submerged in water at 27°C to prevent sample dehydration.

measured with a ruler and recorded. The deflection is subsequently recorded at periodic intervals. For more rigid materials these tests may be conducted over several weeks or even months, but for softer materials such as hydrogels the tests are normally of shorter duration and terminated when the sample fails. These studies were terminated at 24 hours.

4.4.3 Results

Creep may be defined as progressive deformation under constant stress, and testing creep generally involves measuring the dimensional changes that occur as a function of time. The simple creep-rupture experiments designed for this study are different in that the tests are designed to terminate in failure of the specimen. Data from these experiments may be employed to calculate the creep compliance or to predict mechanical performance under long-term cyclic loading. This information may then be used to evaluate materials for a particular application, assist in designing components, or to estimate the dimensional changes that would occur under expected use conditions. There are many established procedures that deal with the creep of plastics and other materials in tension, compression, flexure, and even torsion. However, none of these standards are designed to deal with the unique challenges presented by hydrogel materials or other swelled polymers. ASTM D-2990 was reviewed prior to designing the experiments performed in this section, but the particular requirements of the standard were not followed.

The creep results are shown in Table 4.4 and Figures 4.16 - 4.20. Before reviewing this data it is important to note that each of the data points is based on a single specimen so definitive conclusions about performance cannot be developed. It is also important to

recognize that these values include the initial length of the specimen, so a recorded creep extension of 150% actually represents a 50% ($\varepsilon = 0.5$) extension over the original length. Taking these exceptions into consideration, there are still some interesting comparisons to be made among the materials. In particular, the creep-elongation values are much lower than the values recorded during the tensile tests. Because the time frame of tensile studies is highly compressed relative to creep studies, there is less time for flaws to propagate through the material before flaw-induced failure occurs. In contrast, creep is a relatively slow process which allows the development of flaw-induced failure before natural tensile rupture occurs. Creep-rupture values are therefore more sensitive to flaw distribution in the material. Rupture failure occurred only in the HEMA-based materials. The IPN30 gel failed outside the time frame of the study, while the PVA-S-1 gel exceeded the extension capacity of the test apparatus. The PVA-F-1 gel reached an extension 'plateau' and never failed.

Table 4.4 Creep experiment results based on single samples. Experiment was designed to continue for twenty-four hours unless terminated due to sample failure.

Designation	Mass	Total Elongation (%)							
		0hr	1hr	2hr	4hr	6hr	8hr	12hr	24hr
HR	**750g**	144	157	163	171	-	-	-	-
HN4030G	**350g**	162	165	166	167	167	-	-	-
IPN30	**200g**	169	191	196	199	202	204	208	220
PVA-S-1	**100g**	160	188	207	238	270	322	-	-
PVA-F-1	**900g**	150	153	153	154	154	154	155	156

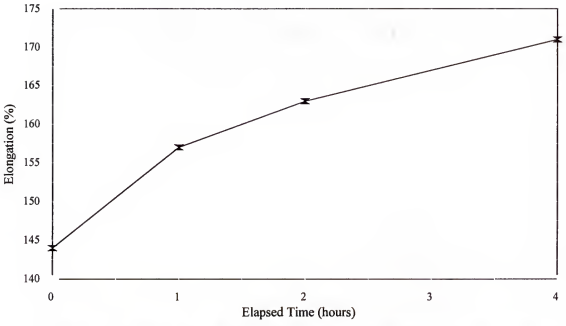

Figure 4.16 Single sample creep experiment results (n=1) for poly(HEMA) hydrogel. The test ended after five hours when the sample ruptured.

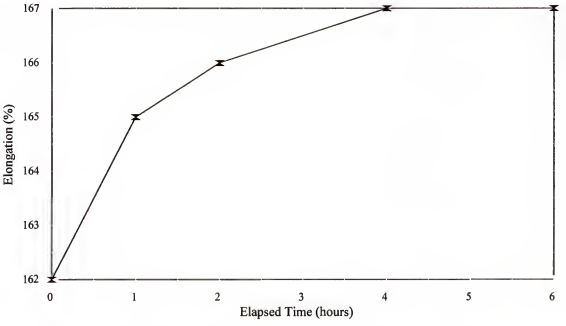

Figure 4.17 Single sample creep experiment results (n=1) for HN4030G copolymer gel. The test ended after eight hours when the sample ruptured

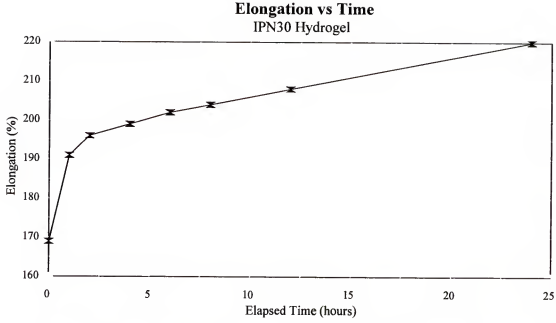

Figure 4.18 Single sample creep experiment results for IPN30 gel. The test was terminated after twenty-four hours without sample failure.

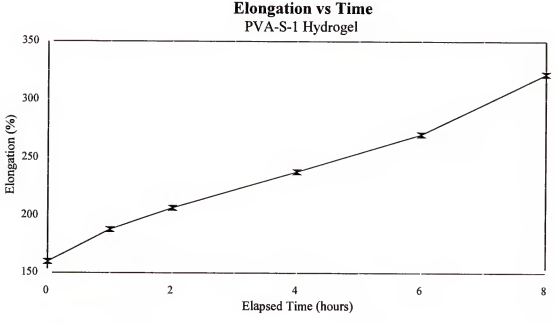

Figure 4.19 Single sample creep experiment results for PVA-S-1 gel. The test ended after eight hours when the sample ruptured.

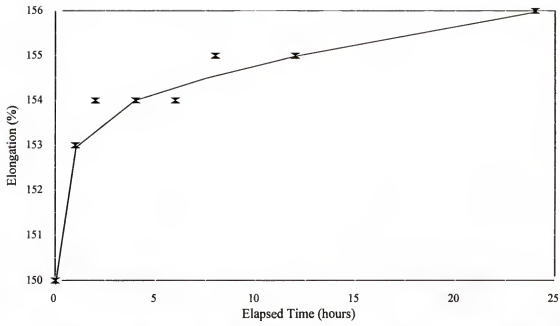

Figure 4.20 Single sample creep experiment results for PVA-F-1 gel. The test was terminated after twenty-four hours without sample failure.

4.5 Summary

It is sometimes necessary when designing gel materials for a specific application to choose between favoring mechanical performance and surface properties. In applications requiring higher strength a material with low water content may be prescribed. However, because most of the beneficial properties attributed to these materials are associated with high water content the surface characteristics of this material will be far from ideal. The effective design of hydrogel materials is therefore contingent on knowledge of the application in question so that a proper balance between surface properties and mechanical performance may be achieved. Commonly employed methods for improving strength include crosslinking and the inclusion of more hydrophobic monomers. Unfortunately, these methods tend to reduce the water content so flexibility and wettability are negatively impacted. In

practice, hydrogel materials with a water content greater than seventy percent are expected to be both compliant and exhibit good surface properties, but these materials also tend to be very weak. When the water content is reduced below forty percent these same materials tend to become stronger but are also more rigid with less favorable surface properties. The target equilibrium water content depends on the specific application and host environment, but in general an attempt is made to maximize this value while maintaining acceptable mechanical performance. As a rule of thumb, a balance of surface properties, flexibility, and strength may be achieved by maintaining the water content between forty and seventy percent. However, in order to quantify acceptable performance variations that occur relative to changes in gel composition a series of selection criteria were previously described in this document. In the current chapter several candidate hydrogel materials were examined for conformance with these criteria based on studies of tensile strength, modulus, ultimate elongation, and creep performance. Based on the results of these studies several hydrogel materials were identified as conforming to the criteria and selected for further testing.

CHAPTER 5
HYDROGEL PROTOTYPES

5.1 Introduction

This chapter describes the design and construction of medical devices which incorporate hydrogel materials. These devices are designed specifically for airway maintenance but in principle may be employed in other applications involving the transfer of fluids into or out from the body. In addition, such devices should prove useful in soft tissue contact applications which would benefit from the smooth, lubricious, non-abrasive surface characteristic of hydrogel materials. The devices to be discussed are distinguished from one another by the way in which hydrogel materials are incorporated into the design and will be known as full-tube (FT) and hybrid-tube (HT) prototypes.

5.2 Prototypes

5.2.1 Full-Tube

Full-tube prototypes are essentially one-piece hydrogel tubes. In practice these devices could be inserted into the trachea in a partially hydrated state, allowing the hydrogel to gradually draw moisture from the humidified air and adjacent tissues to complete hydration. The resulting volumetric expansion may then be advantageously employed to

partially occlude the trachea and maintain seal. When this occurs the expansion of the tube creates an interference fit between the device and the tracheal lining, allowing the sealing pressure to be applied through a fluid layer at the device-tissue interface. In principle, the forces applied to the lining would be limited with this type of device because the sealing surface coincides with the interfacial area of the tube. The presence of the hydrogel material should also lessen tissue trauma by reducing friction, abrasion, and cellular adhesion. However, because hydrogel swelling is a time-dependent process, these devices are limited to long-term applications where an immediate seal with the lumen is not required.

The full-tube design is divided into two (Figure 5.1) subclasses, the Type-1 full-tube and the Type-2 full-tube. Both devices feature a substantial, one-piece hydrogel article which extends the entire length of the device. However, the Type-1 FT employs no reinforcement, while the Type-2 FT relies on a centrally located tube to increase stiffness. This central tube is designed to compensate for the flexibility of lower-modulus gels and may be fashioned from PVC, polyethylene (PE), polypropylene (PP), polyurethane (PU), any other plastic, elastomer, or metal product which has reasonable strength and flexibility. This member serves only to stiffen the device as required and does not contact tissue at any point.

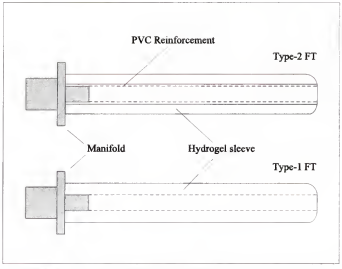

Figure 5.1 Full tube designs. The manifold in the Type-1 FT is bonded directly to the hydrogel article. The manifold in the Type-2 FT is fixed by interference fit. Not to scale.

5.2.2 Hybrid-Tube

Hybrid-tube prototypes are at least partially constructed from hydrogel materials and generally incorporate some form of cuff. In one embodiment these devices resemble standard endotracheal tubes which have been modified with the addition of a hydrogel sleeve. This sleeve may cover an existing cuff or comprise a cuff in and of itself. Unlike full-tube prototypes the presence of the cuff allows these devices to be used in applications which require an immediate seal with the trachea. However, volume swelling of the hydrogel sleeve may also be employed to augment the seal as previously described.

The hybrid-tube design is divided into two subclasses, the Type-1 hybrid-tube and the Type-2 hybrid-tube. Both of these devices (Figure 5.2) feature a one-piece hydrogel sleeve which may or may not extend the entire length of the device. The Type-1 HT employs a sleeve which is bonded at only one location near the machine (proximal) end of a cuffed endotracheal tube. The underlying cuff displaces the sleeve when inflated, and contacts the lining to attain seal. In contrast, the Type-2 HT sleeve is bonded securely in two locations at both the machine end and patient (distal) end of an uncuffed endotracheal tube. The sleeve on this device comprises a true, one-piece

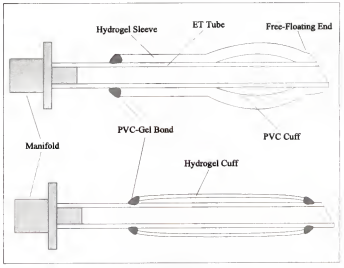

Figure 5.2 Hybrid design tubes. The Type-1 HT (top) is bonded at one end to a conventional Hi-Lo cuffed endotracheal tube. The Type-2 HT (bottom) is sealed in two locations to provide a true hydrogel cuff. This cuff may be filled with air, saline, or any drug-laced fluid. Not to scale.

hydrogel cuff and may be inflated with air, saline, or any other appropriate fluid. The hydrogel material comprises the tissue-contact portion of both devices and serves to reduce tissue trauma by decreasing friction, abrasion, and cellular adhesion.

Hybrid prototypes are ideally employed fully hydrated to take advantage of the increased flexibility and enhanced surface properties characteristic of the swelled state. Because of this the gel-cuff or underlying cuff is generally responsible for achieving and mechanically maintaining seal. However, if desired the devices may also be inserted in a partially hydrated state to allow moisture uptake from the environment. In this case the underlying cuff or gel-cuff must be inflated after insertion to create an initial seal with the lining. Once the hydrogel is sufficiently swelled the cuff may be deflated and the sleeve relied upon to maintain seal with the lining. As previously discussed, this seal is distributed along the entire length of the device so that applied local forces are minimized.

5.3 Assembly

5.3.1 Sleeves

Hydrogel sleeves may be molded in place over existing devices but are more easily fashioned separately. These may be cast in a wide variety of cross-sectional shapes and may have smooth or rough surfaces as specified. In addition, an imprint or shape may be molded into or imparted to the sleeve. The surface of the finished product will conform to the shape of the mold and will generally be affected by the polarity of the mold material. Plastic molds are inexpensive, easily fashioned, and may be used to cast hydrogel articles with intricate surface shapes. However, the hydrophobic surface of commonly employed plastics causes

a reduction in wettability at the surface of the sleeve. Glass molds are more expensive, fragile, and difficult to fabricate, but improve wettability in the finished product. The glass molds employed in this study (Figure 5.3) consist of two coincident borosilicate glass tubes located centrally by silicone ring gaskets. Room temperature curable materials such as PVA and redox initiated gels are cast in the bench top molds, while all others are cast in the submersible molds. The two mold types are essentially identical, but the submersible mold features an open center channel for the passage of warm fluid. The upper gasket locates the center tube but is not sealed, to allow for expansion and the evolution of gas during polymerization.

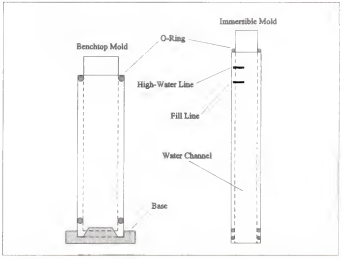

Figure 5.3 Glass tubing molds for casting hydrogel sleeves. The large diameter mold is for casting materials which gel at room temperature. The smaller diameter mold is for casting gels which require a warm water bath. Not to scale.

5.3.2 Bonding

Hydrogel sleeves and tubes may be affixed to existing medical devices by various physical and chemical means, including but not limited to clamping, adhesive bond, solvent bond, and interference fit. In addition, some of these methods may be employed in combination. The method selected will depend on the hydrogel material, the substrate material, and the bond strength required. Hydrogel materials may be bonded to many hydrophobic substrates with a variety of adhesives, but in general those that involve chemical

interaction between the adherends create the strongest bonds. In particular, a group of tube materials including polyvinyl chloride (PVC), polypropylene (PP), polyurethane (PU), latex rubber, and silicone rubber may be bonded to a group of hydrogel materials including those previously discussed using silicone rubber, acrylic, and cyanoacrylate cements. A low-to-medium molecular weight polymer or elastomer dissolved in an appropriate solvent will also serve as an effective adhesive. In practice, any compound that wets both substrates will perform adequately if used in conjunction with a partial interference fit.

Bonding may frequently be accomplished by the application of suitable solvents to encourage intermingling of the adherends while the they are in contact. Mutual diffusion of two surfaces in contact with a common solvent may allow effective bonds to develop even in the absence of interference. In fact, by employing a water soluble co-solvent it is possible to affix a hydrated sleeve directly to an existing hydrophobic medical device. For example, conventional PVA hydrogels may be bonded to PVC medical devices by this method because one of the potential gelling agents (dimethyl sulfoxide) is also an effective solvent for the PVC. By bringing these two components together in the presence of the mutual solvent the PVA hydrogel and PVC polymer interface becomes diffuse. Entanglements subsequently develop and eventually result in a bond whose strength is determined by the amount of solvent employed, the size of the contact area, and the contact pressure. Increasing any of these values will generally improve the quality of the bond.

An optional step in the bonding process involves the use of suitable solvents to diffuse a hydrogel precursor (such as a polyester) into the bulk and onto the surface of the substrate device. Subsequent hydrolysis may then be employed to convert the precursor to

the associated polyol. This not only improves wettability at the surface but also creates potential attachment sites for chemical bonding agents. For example, when a PVC article swelled in DMSO is immersed in a suspension of PVAC (polyvinyl acetate) in chloroform the suspended polymer will spontaneously diffuse into the PVC article. Subsequent hydrolysis then converts a portion of these acetate groups to hydroxyl groups, essentially coating the surface with partially hydrolyzed PVA. Ultimately, this improves wettability as evidenced by a decrease in water contact angle and may be employed as an intermediate step to improve the bond efficacy between the gel sleeves and PVC components.

A combination adhesive-interference process (Figure 5.4) may be employed to affix many hydrophilic gel materials to more hydrophobic substrate plastics. This procedure involves dessication of the gel bond section followed by adhesive application and sealing. In order to prevent overall dehydration and subsequent material degradation the center section of the sleeve is protected during dehydration with a plastic barrier. This allows the end-sections of the sleeve to transform into a xerogel conformation while the center section remains hydrated. The strength of the bond is greatly enhanced if both surfaces are slightly roughened and solvent cleaned prior to bonding. Strength is also improved if the bond section of the gel is heated

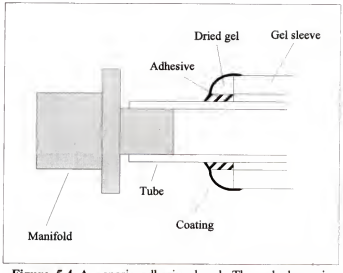

Figure 5.4 A generic adhesive bond. The gel sleeve is attached to the underlying tube using a combination of interference and adhesive. A coating protects the xerogel against rehydration. Not to scale.

prior to bonding. This drives off the water layer at the surface and allows the adhesive to better wet both materials. During dehydration the hydrogel sleeve or tube must be placed on a flexible mandrel to allow the lumen to shrink to the appropriate size. A flexible adhesive such as silicone rubber is then applied to both surfaces before they are pressed together. A waterproof coating (polyurethane) is subsequently applied over the glassy portion of the assembly to protect the bonded region from weakening due to rehydration.

5.4 Applications

Full-tube and hybrid-tube devices differ from commercially available designs in the substantial use of structural hydrogel materials. These devices are designed to be employed primarily in tube, drain, and catheter applications. However, these devices should also prove useful in other applications which would benefit from the smooth, lubricious, non-abrasive, and non-adhesive surface characteristic of hydrogel materials. These devices may be advantageously employed in any situation involving the transfer of fluids into or out from the body, including but not limited to airway maintenance, drug delivery, dialysis, and cavity drainage. Specific device applications include, but are not limited to endotracheal tubes, tracheotomy tubes, nasopharyngeal tubes, nasogastric tubes, chest tubes, wound drains, intravenous catheters, urinary catheters, stents, and shunts.

Full-tube and hybrid-tube devices may facilitate the systemic or local delivery of chemical agents. The integral hydrogel tube or sleeve may be loaded with or bonded to chemical agents including but not limited to antiseptics, antibiotics, anti-inflammatory agents, and anti-thrombogenic agents. If desired, these agents may also be delivered from

microspheres which are incorporated into the hydrogel article. Alternatively, these agents may be loaded into the bulk of the hydrogel or chemically bonded to the device at any internal or external surface. The Type-2 hybrid design has the additional ability to deliver agents from an internal cavity (the gel cuff) by diffusion. Surface loaded agents have no associated delivery rate as they are subject to interactions only at the point of bonding. Bulk loaded agent delivery rates may be controlled by manipulating the chemical composition of the delivered agent and hydrogel, as well as hydrogel morphology and porosity. Delivery rates for the Type-2 hybrid are additionally affected by hydrogel water content, sleeve porosity, drug concentration, and cuff pressure.

5.5 Summary

After bonding the dissimilar hydrophilic and hydrophobic components the prototype devices are essentially complete. However, the xerogel sections which were dehydrated during bonding frequently develop sharp outer edges which may require chamfering with a hand file. Subsequent wet sanding may further improve the appearance of the finished product, but will generally necessitate an additional drying procedure. Once the offending edges are smoothed out and the bond surfaces dried the xerogel sections must be sealed against moisture. This is necessary to prevent rehydration which could weaken the sleeve-tube bond and is readily accomplished with spray-on polyurethane or silicone rubber. The fully hydrated portion of the sleeve or tube is delicate and requires no maintenance. This processing does not affect the overall performance of the device.

CHAPTER 6
MECHANICAL SIMULATION

6.1 Introduction

The complications associated with tracheal intubation are related to the abrasive action of the cuff, cellular adhesion, and high shear and normal forces. However, as stated previously the effect of these complications may be reduced or eliminated by employing an airway device constructed from hydrogel materials. Support of this assertion would require an elaborate multi-part study including material selection, device fabrication, tissue studies, and animal trials. Material selection and device fabrication have been previously discussed, while tissue and animal issues have yet to be addressed. Mechanical simulation is relatively inexpensive and a logical intermediate step toward tissue and animal trials. The design and execution of simulation experiments is the focus of this chapter.

6.2 Tracheal Model

The most commonly employed tracheal model in use today , the 'D-shaped' PVC tube specified in ANSI Z79.14-83, has been replaced by a simpler device. The current standard specifies a smooth glass tube with circular cross section (described in ASTM F1242-89). These devices are attractive to industry because of low cost, but they do not

accurately model tracheal structure. A realistic model must imitate not only the general shape of the trachea, but also mechanical performance and function. To this end, a mechanical model (Figure 6.1) has been devised which imitates the three main components of the trachea. These are the superstructure (polypropylene rings), the basement tissues (latex-gel assembly), and the mucosal lining (PVA hydrogel sleeve). The rubber sleeve, keys, and machine adapter are commercially available. The polypropylene cage and patient adapter must be molded, machined from stock, or cut from tubing. The design as shown employs six 1 cm wide rings equally spaced at 1 cm intervals. The ring edges must be beveled to prevent unnecessary wear on the gel lining. Once the components are assembled, the machine adapter

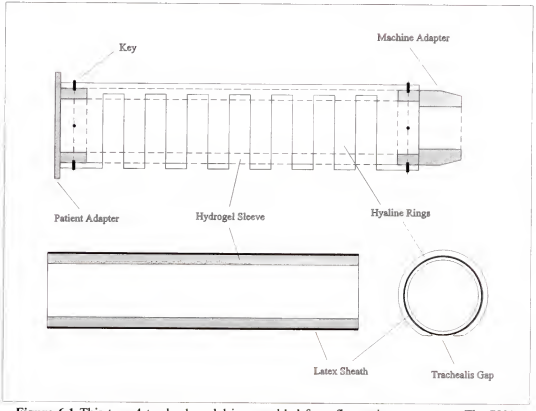

Figure 6.1 This type-4 tracheal model is assembled from five main components. The PVA hydrogel sleeve is positioned inside a latex sheath and the assembly placed into the polypropylene cage. The two adapters are then fitted and fixed in place with stainless steel keys. The machine adapter connects to the mechanical lung, and is normally sealed and fixed permanently in place. Not to scale.

is sealed with silicone or polyurethane and the machine keys fixed with epoxy. Monitoring the condition of the hydrogel sleeve is important because it forms the interface with the endotracheal tube. Modulus values for these materials appear in Table 6.1

Table 6.1 Tensile modulus of the materials used in the construction of the hydrogel tracheal model. Values for some important human and animal tissues are listed as well.[26]

Material	Tensile Modulus
Tracheal Cartilage	20 MPa
Intercartilaginous Tissue	75 KPa
Canine R.A. Muscle	65 KPa
PVA Hydrogel	40 KPa
Poly(propylene)	1000 MPa
Latex Rubber	2.5 MPa

6.3 Simulation

6.3.1 Applied Pressure

A series of experiments were performed to simulate the performance of full-tube airway devices under actual use conditions. These experiments were designed to prove the full-tube capable of maintaining seal and also demonstrate differences in applied pressure between prototype and conventional devices. To this end, a simulator was assembled using

a mechanical lung and the hydrogel tracheal model. The model was instrumented with a Millar catheter transducer and wired to a polygraph so that CT pressure could be monitored and recorded. The simulator (Figure 6.2) was then intubated and ventilated with a Bear 2000 ventilator. Both a Type-1 full-tube and a Mallinckrodt 6 mm ID Hi-Lo cuffed endotracheal tube were tested under identical conditions. Two experiments were performed for each tube simulating healthy lung (high compliance) and stiff lung (low compliance) conditions. For each experiment a tidal volume of 700 ml was delivered to the simulator at 37°C and 100% R.H. The airway pressure and flow rate were monitored with a Bicore respiratory monitor while the CT pressure was measured and recorded on the polygraph. As expected, a

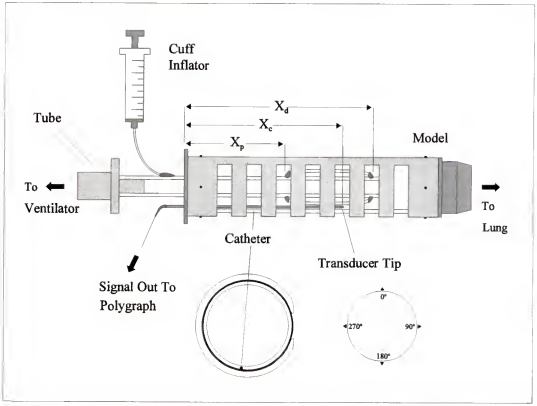

Figure 6.2 Tracheal simulator. Both the conventional tube and the hydrogel tube were tested at high and low compliance under identical conditions. Not to scale.

significant difference in applied pressure was noticed between the ordinary tube and the hydrogel tube. In fact, referring to Figure 6.3 it may be seen that no pressure was transmitted to the tracheal wall by the hydrogel tube at high compliance, with a minimal pressure increase occurring as the lung stiffened. In contrast, the conventional endotracheal tube exerted a measurable pressure on the model even at low compliance. This pressure was multiplied many times as the lung compliance decreased.

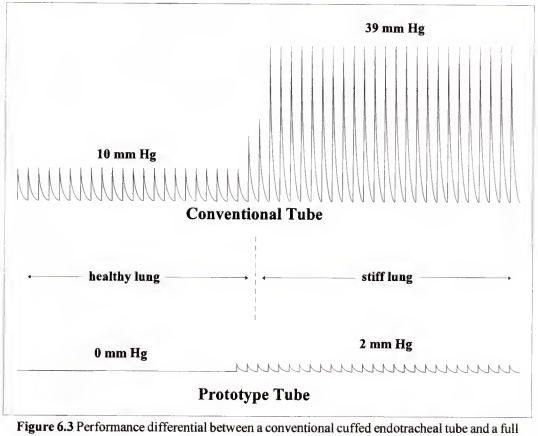

Figure 6.3 Performance differential between a conventional cuffed endotracheal tube and a full tube prototype under identical ventilation parameters. Cuff-to-trachea (CT) pressure varies cyclicly between 0 mm Hg and peak (values listed on graph) as the ventilator fires. There is an obvious performance difference between the two devices.

6.3.2 Prototype Durability

A second series of experiments were devised to test the durability of the hybrid prototypes and to model their effect on the trachea in a simulated intubation. A new tracheal simulator was assembled using the same mechanical lung but employing a new flexible tracheal model. This model featured a very soft inner PVA hydrogel lumen to imitate the mucosal membrane and serve as an interface with the tested airway devices. This lumen was designed to be a 'snap-in' component, easily replaced to avoid long delays between tests. The simulator was also upgraded with a simple linkage to provide relative motion (sliding contact) between the model and the airway device, as well as a 37°C water bath to keep the hydrogel model and prototypes hydrated during the experiments.

Each experiment involved intubating the simulator with either an 8mm ID Mallinckrodt Hi-Lo PVC endotracheal tube or a Type-1 IPN hybrid built on an identical tube. The simulator was ventilated at normal lung compliance with a 700 ml tidal volume while the airway was maintained at 37°C and 100% R.H. with a 5% leak. At regular intervals the experiment was temporarily interrupted so that the condition of the airway device and model could be inspected visually. Both the model and airway device were then graded on a scale from (0 - 4) for severity of damage. A zero value was given in the case of no visible damage, a value of one was assigned at the first appearance of damage, and so forth. An explanation of this grading scale is given in Table 6.2.

Both the hybrid and conventional tubes were tested over a three day period. During this time it became evident that the conventional tube had a pronounced effect (Table 6.3) on the simulator. In fact, even at the relatively benign settings of normal compliance this tube

quickly began to destroy the PVA sleeve in the tracheal model. Mild damage was evident at first inspection (one hour) and possibly occurred much sooner (almost immediately). This damage continued to escalate rapidly until the third day, when the first test was terminated. At this time the hydrogel sheath in the model was changed and the test restarted with the hybrid design tube.

The hybrid tube was tested under conditions identical to the first experiment. The test duration remained the same and inspections were performed at the same time points. However, unlike the conventional tube the Type-1 hybrid had no apparent effect on the tracheal model. Both the IPN sleeve on the hybrid tube and the PVA sheath in the model were assigned zero grades for the entire duration of the test. This result illustrates the large difference between the two devices to potentially cause abrasive damage. This result also suggests that the conventional cuffed tube is much more likely to cause abrasive injury in a real tracheal environment than the hydrogel-sleeved tube.

Table 6.2 Description of grading scale for hybrid tube simulation.

Grade	Comments
0	No visible damage
1	Slight haziness on moist hydrogel surface
2	Mild compression or scratches
3	Deep compression, indentations, or scratches
4	Model or sleeve bursts. Complete erosion through wall.

Table 6.3 Results for normal-compliance simulation of an 8mm ID conventional tube and an 8mm ID Type-1 hybrid tube. Note that the lubricious nature of the hydrogel sleeve decreased friction and prevented any abrasive damage from occurring in the second test.

Device	Area	Time Points (hours)						
		1	3	6	12	24	48	72
Cuffed PVC Tube	Tube	-	-	-	-	-	-	-
	Model	1	1	2	2	3	3	3
Hydrogel Tube	Tube	0	0	0	0	0	0	0
	Model	0	0	0	0	0	0	0

6.3.3 Destructive Testing

A third series of experiments were performed to test the durability of the Type-2 hybrid prototypes and to model their effect on the trachea in a simulated intubation. The simulator was assembled as before with the flexible tracheal model and the mechanical lung set at low compliance to make the test more severe. Each experiment involved intubating the simulator with either an 8mm Mallinckrodt Hi-Lo endotracheal tube or a Type-2 IPN hybrid built on an identical tube (with the cuff removed). The simulator was ventilated with a 700 ml tidal volume at 37°C and 100% R.H. Every attempt was made to maintain the leak at 5%, but because of the low compliance situation the airway pressure was very high and the leak would often vary between 0 and 15%. At regular intervals the experiment was temporarily interrupted so that the condition of the airway device and model could be visually inspected. Both the model and airway device were then graded at that time for severity of damage.

The experimental results (Table 6.4) were striking. The conventional cuffed tube caused severe damage to the model immediately and completely destroyed the hydrogel sleeve before the first 24 hour period had expired. In contrast, the Type-2 hybrid device caused only minor damage to the model, and in fact this did not even develop until near the end of the experiment. This damage may be considered insignificant in light of the severe nature of the test. The large sleeve size and the lubricious nature of the hydrogel surface obviously provide an interface which minimizes damage.

Table 6.4 Results for low-compliance simulation (8 mm ID conventional and 8 mm ID Type-2 hybrid). The conventional endotracheal tube destroyed the model almost immediately, while the hydrogel tube had a very limited impact on the model and was not damaged itself.

Device	Area	Time Points (hours)								
		1	2	3	4	8	12	24	48	72
Cuffed PVC Tube	Tube	-	-	-	-	-	-	-	-	-
	Model	2	2	3	3	3	4	-	-	-
Hydrogel Tube	Tube	0	0	0	0	0	0	0	0	0
	Model	0	0	0	0	0	0	0	1	1

6.4 Summary

Mechanical simulation is an intermediate step in the progression of research from prototype fabrication to animal trial. In fact, simulation serves not only to test the

assumptions on which the study is based but also to validate prototype designs and the materials of fabrication. For this study, a mechanical simulator was devised to model the interaction between the tracheal environment and the airway device. This simulator includes the means to model lung stiffness, adjust ventilation parameters, and monitor applied pressure and total wear in the tracheal lining. A series of experiments was performed with the aid of this equipment at both low and high lung compliance, on both conventional and prototype airway devices. During these experiments all ventilation parameters were maintained at medically acceptable levels and the model lining was monitored for wear.

Both the hydrogel prototypes and conventional devices survived these experiments intact even during extended intubations at elevated pressure. This fact serves to validate the design of the prototype devices and the hydrogel materials from which they were fabricated. In addition, a number of interesting discoveries resulted from these experiments. First, it was discovered during these trials that damage to the tracheal lining was greatly reduced when modeling the hydrogel prototypes relative to conventional devices. Next, it was learned that the pressure transmitted by the full-tube hybrid prototype to the lining was greatly reduced relative to convention devices. Finally, it was found that a great deal more abrasive damage was caused by conventional tubes than hydrogel prototypes as evidenced by visual inspection of the post-simulation hydrogel sheath. From these facts it may be concluded that the hydrogel prototypes are mechanically less damaging to the tracheal lumen than a comparably sized conventional cuffed endotracheal tube.

CHAPTER 7
TISSUE STUDIES

7.1 Introduction

Material interactions with soft tissues are vitally important because these organs are fragile and prone to injury. Design issues aside, materials which perform adequately in one situation may prove inadequate or actually cause harm in more critical applications. For this reason, material selection is one of the fundamental issues of medical device design. In general, when selecting a material for a particular application the medical device engineer may be concerned with bulk mechanical properties, surface characteristics, long-term stability, or other issues. In particular, for the prototype devices currently under investigation the critical material issues have been identified as strength, flexibility, swelling kinetics, and tissue interaction. Mechanical and swelling performance have been previously discussed. This chapter describes tissue interactions with certain candidate hydrogel materials.

7.2 Cell Cultures

The cell culture experiments involve placing material disks in contact with immortal non-fibroblastic human bronchial epithelium. These samples are maintained in appropriate nutrient medium under controlled environmental conditions. During the tests the sample

disks are allowed to set in the medium for a specified time interval after which they are removed and the cell wells trypsinized. The wells are then stained with methyl blue and examined under an optical microscope. This allows the growth and morbidity of the cells to be examined and compared with a control. Four parameters are measured for each experiment ; the number of living and dead cells in the sample well, and the number of living and dead cells in the control well. These experiments are designed to uncover differences in cellular adhesion and toxicity. The materials under investigation include IPN hydrogel, PVA hydrogel, and PVC. By comparing the in vitro performance of these materials it is believed that some conclusions about in vivo performance may be drawn.

The use of methyl blue allows a distinction to be made between living and dead cells by staining the dead cells blue. A biologically inert material is expected to have no effect on the culture, while cells are likely to adhere to or be destroyed by a biologically active or toxic material. In fact, if the material in the test well is inert then the living and dead cell counts should be statistically similar to the control values. A large number of dead cells is evidence of material toxicity, while a large difference in living cell count between the test and control wells may be an indication of adhesion phenomenon. Since the dead cells are easily identified by the blue stain, it may be assumed that the missing cells have migrated into or are adherent to the sample disk.

The results for cell cultures on PVA hydrogel (85% water content), PVP-HEMA IPN hydrogel (60% water content), and Mallinckrodt PVC (cuff material) appear in Tables 7.1 and 7.2. Because the cells counted are those remaining in the well (not adhering to the disk) it is obvious from these results that the hydrogel materials suffer less from adhesion

phenomenon than the PVC cuff material. In fact, the number of living cells in the PVC well diminish to zero almost immediately. Since the cells in this well are not being destroyed they must be adhering to the removed disk. In contrast, the total number of counted living cells for both hydrogel materials more closely follow the control values. The PVA hydrogel in particular appears to almost mirror the performance of the control.

Table 7.1 Sampled living cell count. Wells are inspected under a light microscope so that cells may be counted in three randomly placed views (n=3). Values presented ($\mu \pm \sigma$) are not total well count but are useful for comparison between materials.

Days	Control	PVC	IPN	PVA
0	10.3 ± 4.8	-	-	-
1	23.0 ± 6.4	9.0 ± 6.2	5.7 ± 0.3	13.7 ± 2.1
5	158.0 ± 62.4	0.0 ± 0.0	107.7 ± 31.4	204.0 ± 44.7
7	312.0 ± 140.7	0.0 ± 0.0	71.0 ± 39.9	296.3 ± 74.3

Table 7.2 Sampled dead cell count. Wells are inspected under a light microscope so that cells may be counted in three randomly placed views (n=3). Values presented ($\mu \pm \sigma$) are not total well count but are useful for comparison between materials.

Days	Control	PVC	IPN	PVA
0	0	-	-	-
1	0	2	0	1
5	13	0	13	8
7	47	0	13	16

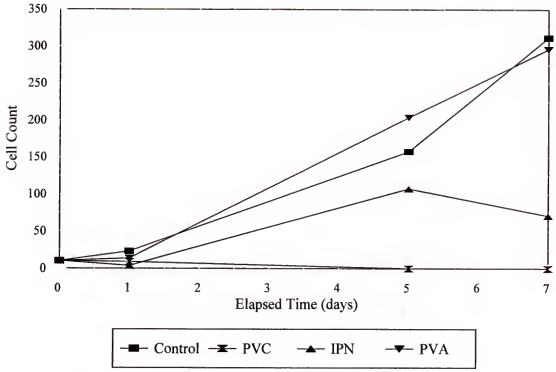

Figure 7.1 Running count of living cells for all test materials.

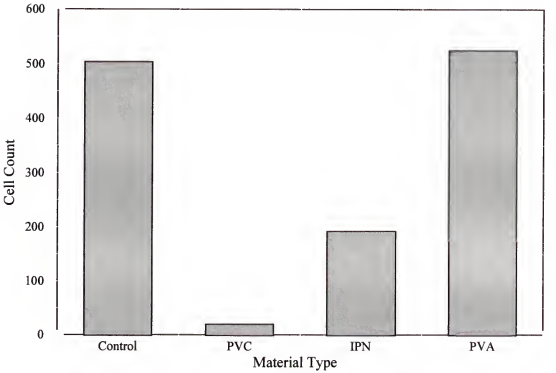

Figure 7.2 Cumulative total count of living cells tabulated over 7 days.

7.3 Animal Studies

Two class B animal studies involving laboratory-bred canines have been completed to date. In the first of these, partial tracheotomies were performed on seven animals to allow the application of artificial constrictions to the trachea. These were applied anterior to the bifurcation in order to artificially increase lung stiffness by restricting flow. This model was employed to compare the performance of prototype and cuffed tubes under 'worst-case' conditions. After intubation with either an HT-2 prototype or conventional tube, the test subjects were ventilated under controlled conditions (tidal volume, humidity, and leak) for 24 hours. The animals were anesthetized for the entire duration of the study after which they were euthanised. The tracheas were then excised, fixed in formalin, and submitted for histological evaluation. This examination did not reveal significant performance differences between device types, but it is believed that the poor condition of the subjects as received may have contributed to the inconclusive results.

The second animal study involved five laboratory-bred canines and did not employ artificial restrictions. In this study, the subjects were ventilated under controlled conditions for 6 hour intervals. Intubation was performed with both conventional tubes and HT-2 (IPN, PVA-S, and PVA-F) prototypes. The subjects remained anesthetized during the initial 6 hour period but were allowed to regain consciousness after extubation. They were then monitored for the ensuing 24 hour period. After this interval the animals were euthanised to allow removal of the tracheas. These were fixed in formalin as before and submitted for histological evaluation. This examination revealed markedly lower injury scores for one of the PVA-F prototypes relative to the control device. Because this result was not repeated for

the other hydrogel device types the results are still considered less than ideal. As before, the pre-study condition of the subjects may have contributed to the inconclusive results.

7.4 Summary

The limited cell culture studies which have been performed to date demonstrate a distinct difference in adhesion performance between the two hydrogel materials tested and ordinary medical grade PVC. In addition, it appears that the vinyl material may be slightly more toxic to the cells relative to the control and two gel materials studied. The standard PVA gel in particular demonstrates a remarkable resistance to adhesion, and it appears that this performance differential becomes more pronounced as the length of exposure continues. Prototype devices fabricated from these materials have successfully passed mechanical simulation, destructive testing, and several 'worst-case' animal trials. However, animal study results have been either mixed or inconclusive to date.

CHAPTER 8
CONCLUSIONS

8.1 Hypothesis

Endotracheal intubation involves the placement of a tube into the tracheal lumen, and is prescribed in any setting in which the airway must be stabilized or the patient anesthetized. The purpose of the endotracheal tube in these procedures is to maintain a viable airway, facilitate mechanical ventilation, allow the administration of anesthetics, and prevent the reflux of fluid into the lungs. In order to satisfy these requirements a nearly airtight seal must be maintained between the tube and the tracheal lining. Most conventional endotracheal tubes provide this seal by employing a cuff that is inflated once the tube is in place. However, the design of this cuff and surface properties of the material are often a source of irritation and injury to the tracheal tissues. In fact, the complication rate for endotracheal intubation is reported to be between 10 and 60%, with manifestations ranging from severe sore throat to erosion through the tracheal wall. These complications are caused by a combination of the materials employed and the forces exerted by the cuff on the tracheal tissues. In particular, the abrasive action of the cuff shears cells from the lining, epithelium adhering to the cuff is removed during extubation, and normal forces exerted on the basement tissues disrupt the blood supply and cause pressure necrosis.

The complications associated with tracheal intubation may be reduced or eliminated by employing airway devices incorporating hydrogel materials. Hydrogels are a class of crosslinked polymers which swell in the presence of moisture, and may contain more than 95% water by weight. Hydrogels are ideal for this application because they are soft and tissue-like, with smooth, lubricous, and non-abrasive surfaces. By placing these materials in apposition to the tracheal lining many of the injuries associated with abrasion, friction, pressure, and cellular adhesion should be significantly reduced. First, an increase in lubricity should reduce the incidence of injury associated with friction and abrasion. Next, a reduction in cellular adhesion should diminish the threat of secondary infection by maintaining the integrity of the tracheal lining. Finally, by employing volume swelling to assist with sealing, a reduction in pressure-related injuries should be realized, especially in the region of the cartilage rings where cuff compression is more pronounced.

8.2 Materials

The hydrogel materials described in this study have been incorporated into several different prototype airway device designs. To satisfy their intended use the component materials in these devices must possess all of the unique properties that have been discussed in previous sections. Hydrogels with high water content will generally be preferred because this tends to enhance flexibility, wettability, and swelling performance. When designing these materials however, a balance must be sought between surface properties, which improve with increased water content, and mechanical strength, which degrades. Ideal materials exhibit superior wettability, smoothness, and lubricity, great strength, and

exceptional elongation while minimizing stiffness. In pursuing this ideal many candidate materials were evaluated in the laboratory on the basis of mechanical properties such as tensile strength, modulus, elongation, and resistance to creep. A secondary consideration was the enhancement of water content, swelling kinetics, and surface finish. Final hydrogel material validation was achieved in the completion of mechanical modeling and destructive testing. The data from these studies was distilled into performance criteria

A performance criteria of 25 psi tensile strength, 20 psi modulus, 50% water content, and 300% ultimate elongation were specified for all hydrogels incorporated into prototype airway devices. First, the strength criterion was based on the mechanical modeling of several gel types. During these trials it was discovered that a tensile strength of 25 psi was sufficient to survive an extended simulated intubation. Next, the elongation requirement was based on an estimate of deformation assuming a low-profile hydrogel cuff was inflated under actual use conditions. This restriction was proven unnecessarily restrictive when materials with elongation values below 300% survived mechanical simulation. Finally, the water content requirement was set to 50% because material surface evaluations indicated that this represented an approximate lower limit for the exhibition of lubricious behavior. It is important to note, however that these criteria were identified in the initial stages of the materials search, and as such served only as a guide and point of reference for second generation materials. In reality, the nominal values of strength, modulus, elongation, and water content required for acceptable performance in real world situations have yet to be determined. Still, several candidate hydrogel materials satisfied these selection criteria and were shown to perform well in mechanical simulations.

8.3 Conclusions

The full-tube and hybrid-tube designs have been validated by repeated mechanical simulation, destructive testing, and tissue trials. In each of these studies the prototypes have survived intact and have equaled or exceeded the performance of commercially available airway devices. The hydrogel materials incorporated into these devices have also been validated by these studies and by the satisfaction of the previously discussed performance criteria as confirmed by extensive experimentation. In terms of mechanical strength, the freeze-thaw PVA materials surpass almost all commercially available hydrogel materials, while the standard PVA hydrogels are highly lubricious with superior surface characteristics. The IPN materials fall midway between these two, and depending on composition may cover a wide range of mechanical, swelling, and surface characteristics. Limited tissue compatibility testing performed on the IPN and standard PVA hydrogels shows that at least these materials are superior to PVC with regards to cellular adhesion. The studies indicate that these materials are in general less offensive to respiratory cells. However, animal studies performed to date have been either mixed or inconclusive, so no concrete statements on the efficacy of the material-prototype combination may be derived.

There is no doubt that the prototypes satisfy their intended use. These devices are indicated for airway maintenance, and in fact these have been shown to successfully maintain the airway over a wide range of operating conditions. In truth, the design was initially validated when the first simulation study was completed. However, the animal studies show that the primary claim of reduced injury has not been verified. Perhaps the animal trials were flawed or the histological examination improperly performed. Perhaps performance

differences did exist but were masked by pre-existing conditions in the test subjects. Perhaps these injuries were unintentionally inflicted by the presence of manufacturing contaminants or pyrogens remaining in the prototypes themselves. Until these questions are answered the results of this study are either mixed or inconclusive. The apposition of a smoother, softer, water-laden interface to the tracheal tissues should by all rights lead to a reduction in complications. However, this still remains to be proven.

8.4 Suggested Research

This study has been remarkably complex, progressing from concept to hydrogel formulation, from mechanical characterization to prototype design, through mechanical simulation to tissue studies and finally to animal trials. However, the work is still incomplete. In light of the apparent inconsistencies between the animal trials and simulation studies, much of the preliminary characterization should be revisited. The materials search should expand to encompass new materials, mechanical and swelling studies should continue, and the tracheal simulator should be refined to more closely mimic real-world conditions. However, the most important addition to these studies would be the completion of tissue and animal trials. First, prototype fabrication should resume in facilities capable of providing sterile and non-pyrogenic production units. Next, tissue trials should expand to include more materials at larger sample sizes to increase the possibility of achieving statistically significant results. Finally. animal studies should resume at a facility capable of insuring the health of the animals at reception, before testing, and during recovery so that positive results may be a realistic expectation from the beginning.

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BIOGRAPHICAL SKETCH

Christopher Sakezles was born in Tampa, Florida, on May 12, 1966. He attended Chamberlain High School where he played baseball, performed in marching band, and served for three years as first chair trumpet in the jazz, symphonic, and marching bands. It was during this time that he developed an interest in machinery and decided to pursue a career in science. After graduating he elected to attend the University of South Florida where he studied mechanical engineering. He excelled at these studies and was invited to join Tau Beta Pi in his third year. Two years prior to receiving his bachelor's degree in 1991 he worked as an engineering intern for Honeywell Space and Strategic Avionics in Clearwater, Florida. In this capacity he was responsible for providing engineering support for the MX missile avionics production line. During the summer of 1990 he was employed as a quality assurance intern for Tredegar Molded Products in St. Petersburg, Florida. He became interested in polymer science at this time and decided to pursue an advanced degree.

Mr. Sakezles enrolled at the University of Florida in 1991. At this time he began working on a project for the U.S. Air Force studying concrete corrosion at stealth aircraft facilities. In the first year of this project he helped to develop a polymer-modified cement that is still being evaluated by the U.S. military. The project culminated in his graduation

with a master's degree in materials science and engineering in 1993. His masters thesis was titled Ester-Related Corrosion in Ordinary Portland Cement Concrete: Time-Dependent Strength Loss in the Presence of Corrosive Media.

Mr. Sakezles began his doctoral studies in 1994. During the following years he worked on a series of research projects funded by Allied Health Care studying the mechanical characteristics of hydrogels and their use in various medical devices. During the course of these studies he developed several novel hydrogel materials, fabrication processes, and medical devices. The project was concluded in 1998 when he received a doctorate in materials science and engineering.

I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

Christopher Batich, Chair
Professor of Materials Science
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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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I certify that I have read this study and that in my opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation for the degree of Doctor of Philosophy.

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This dissertation was submitted to the Graduate Faculty of the College of Engineering and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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